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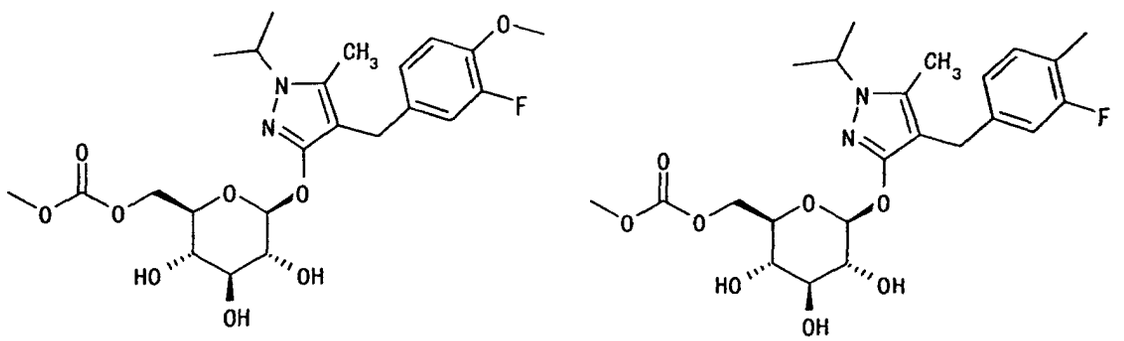
(54) NOVEL PYRAZOLE DERIVATIVES AND DIABETES REMEDIES CONTAINING THE SAME

(57) The present invention provides pyrazole-O-glycoside derivatives represented by the following formulae, used as a diabetic medicine.



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Description

Background of the Invention

[0001] The present invention relates to new pyrazole derivatives and diabetic medicine which have those compounds as an active ingredient.

[0002] Na^+-dependent glucose transporter (SGLT) is a membrane protein which transports glucose, and SGLT-1 and SGLT-2 are known. SGLT-2 mainly expresses in renal uriniferous tubules. Glucose that is filtered in glomeruli is reabsorbed at the renal uriferous tubules via SGLT, and the glucose taken is reused in the body through the bloodstream. When SGLT is inhibited, the amount of the glucose reabsorbed at renal uriniferous tubules lowers, and the glucose is discharged through urine. As a result, it is considered that the level of blood sugar decreases. At the present time, no medicine is clinically used such as that inhibiting reabsorption of glucose in the kidney.

Disclosure of the Invention

[0003] The object of the present invention is to provide new pyrazole derivatives.

[0004] The object of the present invention is also to provide a pharmaceutical composition containing the new compounds.

[0005] The object of the present invention is also to provide a pharmaceutical composition for the treatment of diabetes which comprises the new compound.

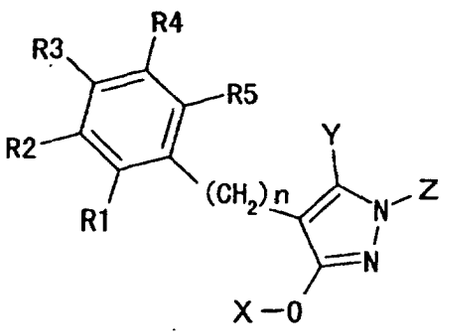
[0006] The object of the present invention is to find and provide diabetic-medicine which is easy to synthesize, less toxic and has higher curative effect.

[0007] The present invention also intends to provide urinary sugar excretion inducers which have the new compounds.

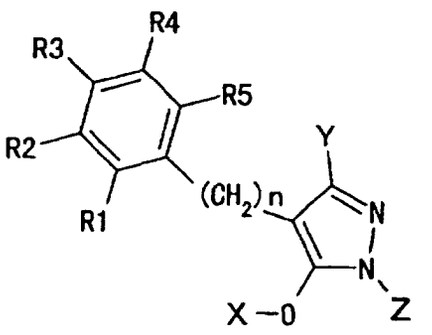
[0008] Further, the present invention intends to provide the use of the new compounds for producing a pharmaceutical composition which reduces renal glucose reabsorption at renal uriniferous tubules.

[0009] The inventors have synthesized various derivatives (1A) or (1B) wherein glucose (namely, β -D-glucopyranose) or glucuronic acid (namely, β -D-glucopyranoside uronic acid) is bonded to pyrazole, and vigorously investigated the action of those derivatives on urinary sugar excretion. As the result of animal tests, they have found that the compounds of general formula (1A) or (1B) have the outstanding action on urinary sugar excretion and completed the present invention. These compounds have not ever been synthesized and, therefore, are completely new pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives.

[0010] Namely, the present invention provides pyrazole derivatives of the following general formula (1A) or (1B) or pharmaceutically acceptable salts thereof:



(1A)



(1B)

wherein X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated or β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated and carboxyl group may be esterified; Y represents a lower alkyl group or perfluoro lower alkyl group; Z represents a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, aralkyl group or phenyl group; R1 to R5 may be the same or different and represent a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, halogeno group, lower alkanoyl group, lower alkenyl group or lower alkynyl group, and n represents an integer from 0 to 3.

[0011] The present invention provides a pharmaceutical composition which comprises the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0012] The present invention also provides a pharmaceutical composition for the treatment of diabetes which comprises the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0013] The present invention also provides urinary sugar excretion inducers which comprise the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof as an active ingredient.

[0014] Further, the present invention provides the use of the above-mentioned pyrazole derivatives or pharmaceutically acceptable salts thereof for producing a pharmaceutical composition which reduces renal glucose reabsorption at renal uriniferons tobules.

Best Mode for Carrying out the Invention

[0015] The term "lower" in the present specification indicates 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. The terms "alkyl", "alkenyl" and "alkynyl" in alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, lower alkanoyl group, lower alkenyl group or lower alkynyl group may be linear or branched.

[0016] An alkyl part in "aralkyl group" in the present specification is a lower alkyl group. An aryl part in "aralkyl group" is a monocyclic or bicyclic aromatic substituent having 5 to 12 carbon atoms.

[0017] Examples of the alkyl group include methyl group, ethyl group, propyl group, butyl group, pentyl group, isopropyl group, isobutyl group and isopentyl group. The perfluoro lower alkyl group is, for example, a trifluoromethyl group. Examples of the lower alkoxy group are methoxy group, ethoxy group, propyloxy group and isopropyloxy group. The perfluoro lower alkoxy group is, for example, a trifluoromethoxy group. The lower alkylthio group includes such as methylthio group, ethylthio group and propylthio group. The perfluoro lower alkylthio group is, for example, trifluoromethylthio group. The lower alkyl amino group includes such as methyl amino group, ethyl amino group, propyl amino group, dimethyl amino group and diethyl amino group. The lower alkanoyl group is, for example, acetyl group and propionyl group. The lower alkenyl group includes such as vinyl group, propenyl group and 2-methyl-1-propenyl group. The lower alkynyl group is, for example, ethynyl group and propynyl group. The aralkyl group includes such as benzyl group, benzyl group of which a benzene ring may have one or more substituents, phenethyl group and phenethyl group of which a benzene ring may have one or more substituents. The substituents of benzyl group and phenethyl group herein include lower alkoxy group, lower alkyl group, halogeno group and halogeno lower alkyl group. Examples of the halogeno group are fluorine atom, bromine atom, chlorine atom and iodine atom.

[0018] The groups for acylating hydroxyl group include acyl group and carbamate group; acyl group includes such as acetyl group, propionyl group, benzoyl group and pivaloyl group; carbamate group includes such as methyl carbonate group, ethyl carbonate group, propyl carbonate group, isopropyl carbonate group and phenyl carbonate group. The groups for esterifying carboxyl group include lower alkyl group such as methyl group, ethyl group, propyl group and isopropyl group.

[0019] In the above-mentioned general formula (1A) or (1B), one or more hydroxyl groups of β -D-glucopyranosyl group which is a group represented by X may be acylated. Especially, one or more hydroxyl groups of the said group may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group. Examples of such groups are 6-O-acetyl- β -D-glucopyranosyl group and 6-O-methoxycarbonyl- β -D-glucopyranosyl group.

[0020] Further, one or more hydroxyl groups of β -D-glucuronyl group which is a group represented by X may be acylated and its carboxyl group may be esterified. Especially, one or more hydroxyl groups of the said group may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group and its carboxylic acid may be esterified with lower alkyl group. An example of such groups is 6-O-methyl- β -D-glucuronyl group.

[0021] The groups represented by X are preferably β -D-glucopyranosyl group, 6-O-acetyl- β -D-glucopyranosyl group, 6-O-methoxycarbonyl- β -D-glucopyranosyl group, β -D-glucuronyl group and 6-O-methyl- β -D-glucuronyl group. Among them, β -D-glucopyranosyl group and β -D-glucuronyl group are more preferable. Particularly, the group represented by X is preferably β -D-glucopyranosyl group of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl groups having 2 to 20 carbon atoms, lower alkoxycarbonyl groups and benzoyl group. It is more preferable that the group is acylated with alkanoyl group having 2 to 6 carbon atoms or lower alkoxycarbonyl group. Among them, one hydroxyl group is preferably acylated. Most preferably, the hydroxyl group connected to a carbon atom at the 6th position is acylated. Examples of such groups represented by X are 6-O-acetyl- β -D-glucopyranosyl group and 6-O-methoxycarbonyl- β -D-glucopyranosyl group.

[0022] The groups represented by Y are preferably lower alkyl group having 1 to 3 carbon atoms or perfluoro lower alkyl group having 1 to 6 carbon atoms. A methyl group and trifluoromethyl group are particularly preferable.

[0023] The groups represented by Z are preferably hydrogen atom and lower alkyl group having 1 to 6 carbon atoms.

A hydrogen atom, lower alkyl group having 1 to 3 carbon atoms, unsubstituted aralkyl group or aralkyl group of which an aryl part at the 4th position is substituted and unsubstituted phenyl group are also preferable. Further, hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, unsubstituted benzyl group or benzyl group of which an aryl part at the 4th position is substituted and unsubstituted phenyl group are more preferable. Among them, hydrogen atom, methyl group, ethyl group, propyl group and isopropyl group are more preferable, and isopropyl group is particularly preferable.

[0024] The groups represented by R1 to R5 are preferably lower alkyl group having 1 to 6 carbon atoms, lower alkylthio group having 1 to 6 carbon atoms, halogeno atom, lower alkoxy group, lower alkenyl group and lower alkynyl group. A methyl group, ethyl group, methylthio group, ethylthio group, fluorine atom, methoxy group, vinyl group, propenyl group, ethynyl group and propynyl group are more preferable. It is particularly preferable that one or two groups represented by R1 to R5 are one of the above-mentioned preferable groups and the rest of the groups are hydrogen atom. In this case, at least R3 is preferably one of the above-mentioned preferable groups. When two groups in R1 to R5 are one of the above-mentioned preferable groups, they may be the same or different from each other, but they are preferably different from each other. Further, when R3 is either lower alkyl group, lower alkoxy group, lower alkenyl group or lower alkynyl group, R4 or R5 is preferably a fluorine atom. It is preferable that one of R1, R2, R4 and R5 is halogeno group, or R1, R2, R4 and R5 are all hydrogen atom and R3 is lower alkyl group, lower alkoxy group, lower alkenyl group or lower alkynyl group. It is also preferable that one of R1, R2, R4 and R5 is a fluorine atom and R3 is methyl group, ethyl group, methoxy group, vinyl group or ethynyl group.

[0025] It is preferable that n represents an integer 1.

[0026] Y in general formula (1A) or (1B) is preferably trifluoromethyl group.

[0027] Further, it is preferable that in general formula (1A) or (1B), Y is trifluoromethyl group and n is 1.

[0028] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

[0029] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group and its carboxylic acid may be esterified with alkyl group.

[0030] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucopyranosyl group.

[0031] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-acetyl- β -D-glucopyranosyl group.

[0032] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-carbomethoxy- β -D- glucopyranosyl group.

[0033] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is β -D-glucuronyl group.

[0034] It is also preferable that in general formula (1A) or (1B), Y is trifluoromethyl group, n is 1 and X is 6-methyl- β -D-glucuronyl group.

[0035] It is also preferable that in general formula (1A) or (1B), X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

[0036] It is also preferable that in general formula (1A) or (1B), X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with lower alkoxycarbonyl group.

[0037] It is also preferable that in general formula (1A) or (1B), Y is lower alkyl group having 1 to 3 carbon atoms or perfluoro lower alkyl group having 1 to 6 carbon atoms; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is a hydrogen atom, lower alkyl group having 1 to 3 carbon atoms, unsubstituted aralkyl group or aralkyl group of which an aryl part at the 4th position is substituted or unsubstituted phenyl group; one of R1, R2, R4 and R5 is a halogeno group, or R1, R2, R4 and R5 are all hydrogen atom and R3 is a lower alkyl group, lower alkoxy group, halogeno group, lower alkenyl group or lower alkynyl group.

[0038] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkyl group and R4 or R5 is a fluorine atom.

[0039] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkoxy group and R4 or R5 is a fluorine atom.

[0040] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkynyl group.

[0041] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is lower alkynyl group and R4 or R5 is a fluorine atom.

[0042] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkenyl group.

[0043] It is also preferable that in general formula (1A) or (1B), Y is a methyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is an isopropyl group; R3 is a lower alkenyl group and R4 or R5 is a fluorine atom.

[0044] It is also preferable that in general formula (1A) or (1B), Y is a methyl group or trifluoromethyl group; n is 1; X is β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z is a hydrogen atom, isopropyl group, aralkyl group or phenyl group; one of R1, R2, R4 and R5 is a fluorine atom and R3 is a methyl group, ethyl group, methoxy group, vinyl group or ethynyl group.

[0045] The compounds or pharmaceutically acceptable salts thereof described below are also preferable:

4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-propylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-isopropylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-methylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-propylphenyl) methyl)-5-(trifluoromethyl)- 1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-isopropylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-vinylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethynylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-methylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-propylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-isopropylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-methylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-ethylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-propylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-isopropylthiophenyl) ethyl)-5-(trifluoromethyl)- 1H-pyrazole-3-O- β -D-glucopyranoside;
4'-((4'-methylthiophenyl) methyl)-5'-trifluoromethyl-3'-O-(6-0-carbomethoxy- β -D-glucopyranosyl)-1H-pyrazole;
4'-((4'-ethylphenyl) methyl)-5'-(trifluoromethyl)-3'-O-(6-0-carbomethoxy- β -D-glucopyranosyl)-1H-pyrazole;
4'-((4'-methylthiophenyl) methyl)-5'-trifluoromethyl-3'-O-(2,3,4,6-0-tetraacetyl- β-D-glucopyranosyl)-1H-pyrazole;
4'-((4'-ethylphenyl) methyl)-5'-(trifluoromethyl)-3'-O-(2,3,4,6-0-tetraacetyl- β -D-glucopyranosyl)-1H-pyrazole;
4-[(4-trifluoromethoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4'-trifluoromethoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-0-tetraacetyl)- β -D-glucopyranoside;
4'-[(4'-trifluoromethoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-[(4-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-[(4-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((3-fluoro-4-methoxyphenyl) methyl)-1'-isopropyl-5'-methyl- 1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyran-

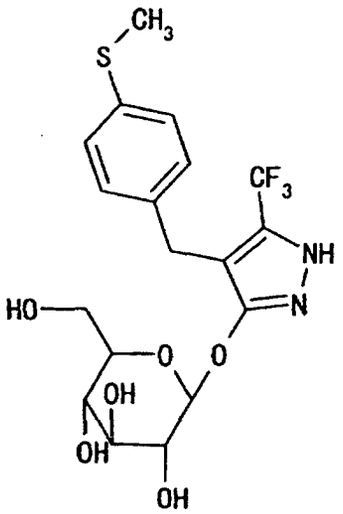
oside;
4'-((3-fluoro-4-methylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((2-fluoro-4-methoxyphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((2-fluoro-4-methylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((2-fluoro-4-ethylphenyl) methyl)- 1'-isopropyl-5'-methyl- 1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((3-fluoro-4-ethylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((4-ethynylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((2-fluoro-4-ethynylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((3-fluoro-4-ethynylphenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((4-(1-propynyl) phenyl) methyl)- 1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((3-fluoro-4-(1-propynyl) phenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4'-((2-fluoro-4-(1-propynyl) phenyl) methyl)-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-((3-fluoro-4-methoxyphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β-D-glucopyranoside;
4-((3-fluoro-4-methylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((2-fluoro-4-methoxyphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β - D-glucopyranoside;
4-((2-fluoro-4-methylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((2-fluoro-4-ethylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-fluoro-4-ethylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethynylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((2-fluoro-4-ethynylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-fluoro-4-ethynylphenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-(1-propynyl) phenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((3-fluoro-4-(1-propynyl) phenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-β -D-glucopyranoside;
4-((2-fluoro-4-(1-propynyl) phenyl) methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-β -D-glucopyranoside;
4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-ethylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-propylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-isopropylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-methylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-propylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-isopropylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-vinylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-ethynylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-methylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-ethylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-propylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((4-isopropylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((3-methylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((3-ethylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((3-propylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-((3-isopropylthiophenyl) ethyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
methyl 4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranouronate; and
ethyl 4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranouronate.

[0046] Among the above-mentioned examples, the following compounds or pharmaceutically acceptable salts thereof are particularly preferable:

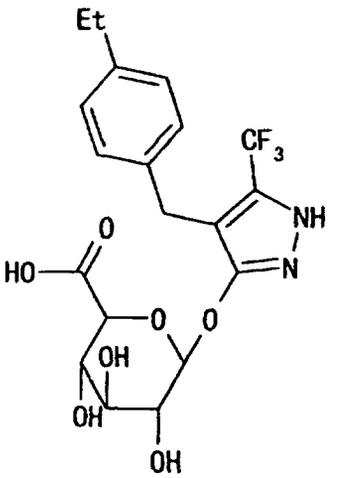
4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;
4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;
4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4-ethylphenyl) methyl]-1'-[(4'-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;
4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β - D-glucopyranoside;
4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β - D-glucopyranoside;
4'-[(2-fluoro-4-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;
4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside; and
4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside.

[0047] Among the above-mentioned examples, the following compounds or pharmaceutically acceptable salts thereof are particularly preferable:



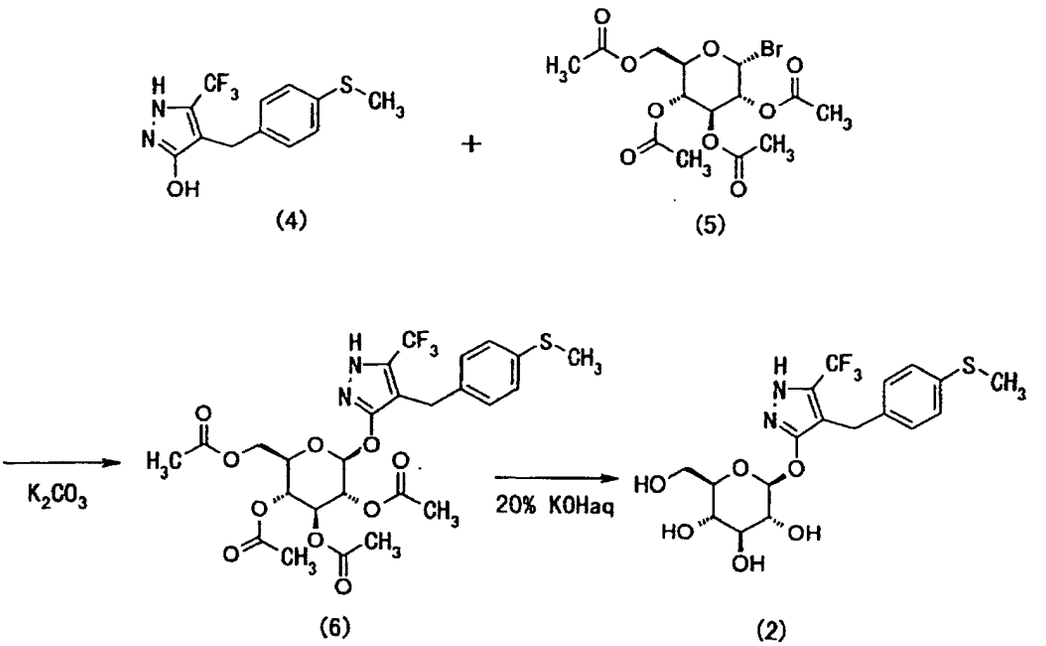
(2)



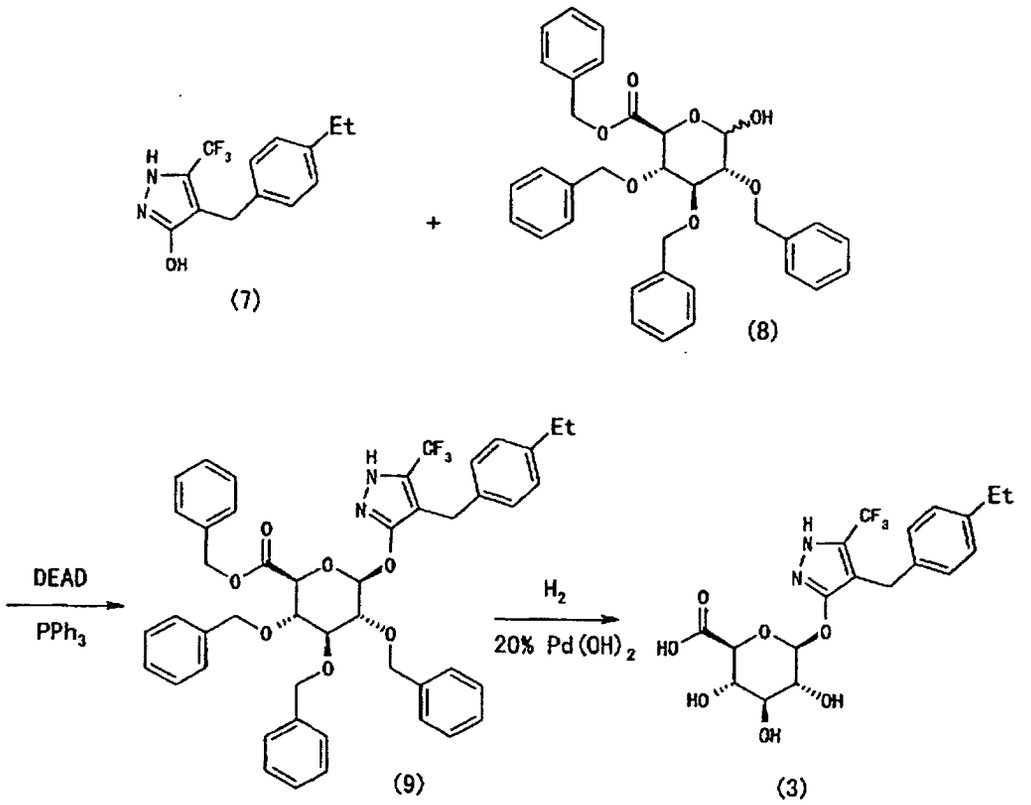
(3)

[0048] The following compounds or pharmaceulically acceptable salts thereof are also preferable:
4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside; and
4-[(4-ethylphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β -D-glucopyranoside.

[0049] As methods for producing pyrazole derivatives (1A) or (1B) in the present invention, for example, the compounds are produced in accordance with methods described below when X is β -D-glucopyranosyl group or β -D-glucuronyl group.

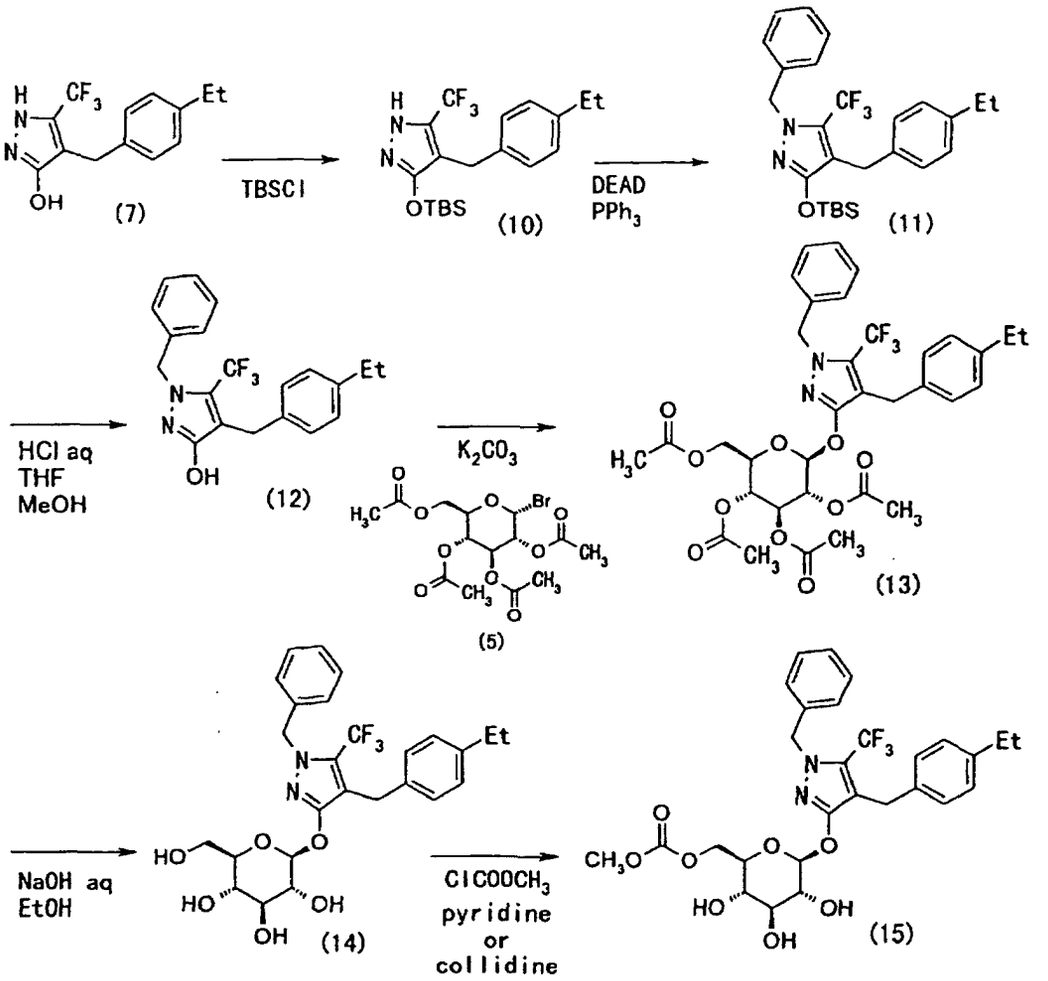


[0050] For example, the compound shown as the compound (2) of the present invention can be obtained by methods described as follows. 1,2-dihydro-4-[(4-methylthiophenyl) methyl]-5-(trifluoromethyl)-3H-pyrazole-3-one (4) (prepared by methods described in J. Med. Chem. 1996, 39, 3920-3928) is reacted with 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide in the presence of potassium carbonate in chloroform-water overnight. The product is purified by using such as the chromatography and tetra-O-acetyl intermediate (6) can be obtained, and then this intermediate is deprotected in a potassium hydroxide aqueous solution to obtain the intended compound (2).

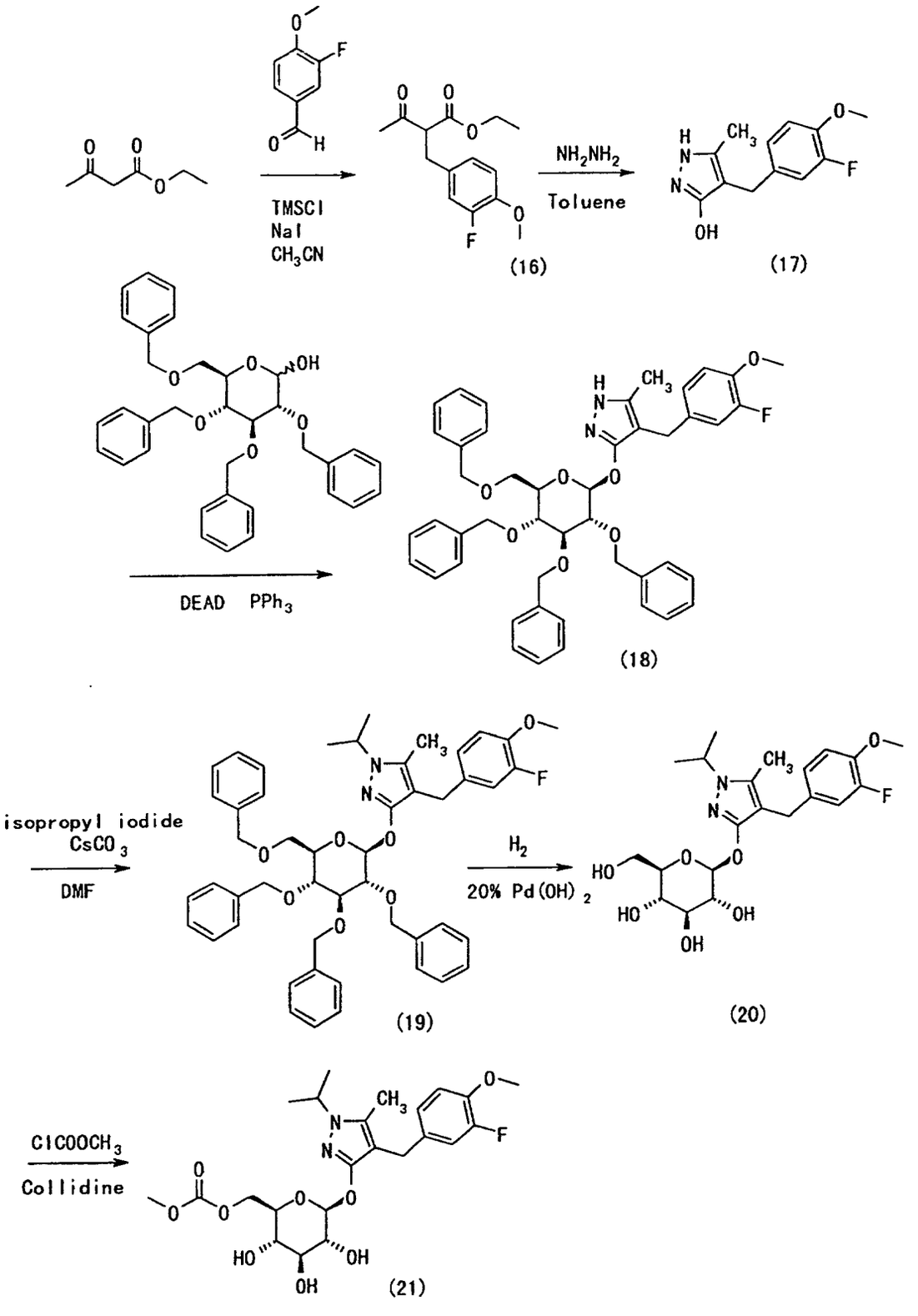


[0051] For example, the compound shown as the compound (3) of the present invention can be obtained by methods described as follows. 1,2-dihydro-4-[(4-ethylphenyl) methyl]-5-(trifluoromethyl)-3H-pyrazole-3-one (7) (prepared by methods described in J. Med. Chem. 1996, 39, 3920-3928) and 2,3,4-tri-O-benzyl-D-glucopyranoside uronic acid benzyl ester (8) are reacted with triphenylphosphane and diethyl azodicarboxylate (DEAD) in tetrahydrofuran for 1.5 hours. The product is purified by using such as the chromatography and tetra-benzyl intermediate (9) can be obtained. Then this intermediate is deprotected under hydrogen atmosphere by 20%$Pd(OH)_2$ to obtain the intended compound (3).

[0052] For example, the compound shown as the compound (15) of the present invention can be obtained by methods described as follows. A hydroxyl group of 1,2-dihydro-4-[(4-ethylphenyl) methyl]-5-(trifluoromethyl)-3H-pyrazole-3-one (7) is protected by tert-butyldimethylsilylchloride to obtain compound (10). Benzyl alcohol is reacted with a nitrogen atom on pyrazole of the compound in accordance with Mitsunobu reaction to obtain (11). TBS group is then deprotected by diluted hydrochloric acid and reacted with 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (5) in the presence of potassium carbonate in chloroform-water overnight. The product is purified by using such as the chromatography and tetra-O-acetyl intermediate (13) can be obtained. Then this intermediate is deprotected in a potassium hydroxide aqueous solution to obtain (14). Aprimary hydroxyl group of the obtained compound (14) is reacted with methyl chlorocarbonate to obtain the intended compound (15).

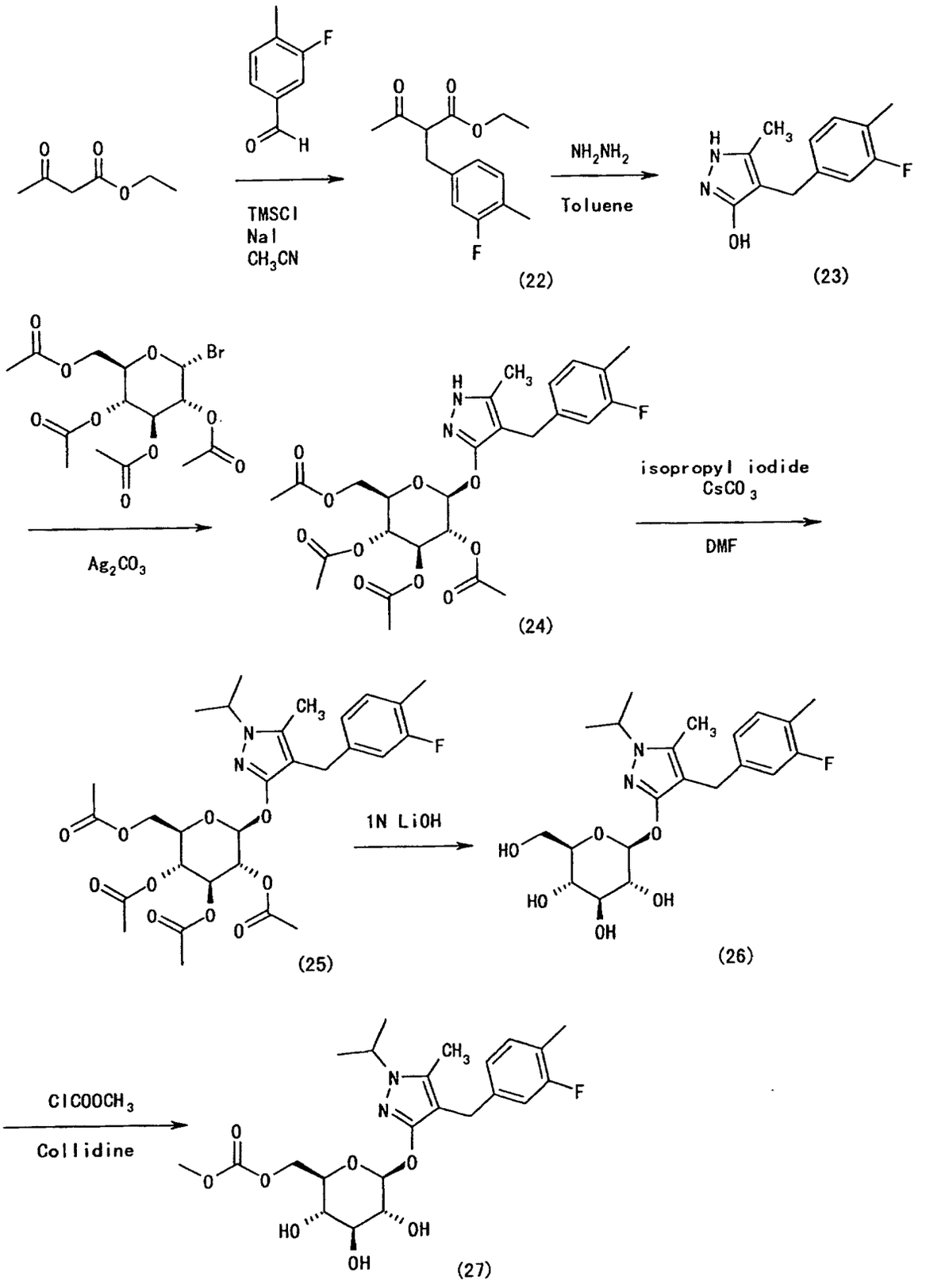


[0053] For example, the compound shown as the compound (21) of the present invention can be obtained by methods described as follows. Ethyl acetoacetate and 3-fluoro-4-methoxybenzaldehyde are reacted with trimethylsilylchloride and sodium iodide in acetonitrile to obtain an intermediate (16) and by forming a ring structure with hydrazine, 1,2-dihydro-4-[(3-fluoro-4-methoxylphenyl) methyl]-5-methyl-3H-pyrazole-3-one (17) can be obtained. Then, 2,3,4,6-tetrabenzylglucopyranose is reacted with a hydroxyl group on pyrazole thereof in accordance with Mitsunobu reaction to obtain (18) and a nitrogen atom in the 1st position of pyrazole thereof is isopropylated by cesium carbonate and isopropyl iodide to obtain compound (19). A benzyl-protecting group of (19) is deprotected under hydrogen atmosphere by 20%$Pd(OH)_2$ to obtain compound (20), and a hydroxyl group at the 6th position of (20) is reacted with methyl chlorocarbonate in collidine to obtain the intended compound (21).



[0054] For example, the compound shown as the compound (27) of the present invention can be obtained by methods described as follows. Ethyl acetoacetate and 3-fluoro-4-methylbenzaldehyde are reacted with trimethylsilylchloride and

sodium iodide in acetonitrile to obtain an intermediate (22) and by forming a ring structure with hydrazine, 1,2-dihydro-4-[(3-fluoro-4-methylphenyl) methyl]-5-methyl-3H-pyrazole-3-one (23) can be obtained. Then, 2,3,4,6-O-tetraacetyl-α-D-glucopyranosyl bromide is reacted with hydroxyl group on pyrazole thereof by silver carbonate to obtain (24) and a nitrogen atom at the 1st position of pyrazole thereof is isopropylated by cesium carbonate and isopropyl iodide to obtain compound (25). An acetyl-protecting group of compound (25) is deprotected by 1N LiOH to obtain compound (26), and a hydroxyl group at the 6th position of compound (26) is reacted with methyl chlorocarbonate in collidine to obtain the intended compound (27).



[0055] Pyrazole-0-glycoside derivatives and pyrazole-0-glucuronide derivatives of the present invention produced by the above-mentioned methods can be easily isolated and purified from the reaction mixture by ordinary methods

for isolation and purification, such as the extraction by solvents, chromatography and crystallization.

[0056] A hydroxyl group of the compounds of the present invention may be substituted with appropriate substituents which are exchanged to a hydroxy group in vivo. The substituents of hydroxyl group are, for example, acyl group and carbamate group. An acyl group includes such as alkanoyl group having 2 to 20 carbon atoms and benzoyl group and carbamate group includes such as lower alkoxycarbonyl group. Especially, the substituents of hydroxyl group of glucopyranosyl group are preferably carbamate group which is lower alkoxycarbonyl group and more preferably methoxycarbonyl group. A carboxyl group of the compounds of the present invention may be substituted with appropriate substituents which are exchanged to a carboxyl group in vivo. The substituents of carboxyl group are, for example, lower alkyl group such as methyl group and ethyl group.

[0057] When the compounds shown in general formula (1A) or (1B) of the present invention can form salts thereof, the salts should be pharmaceutically acceptable. When an acidic group exists in the formula, the salts to the acidic group include such as ammonium salt; salts of alkali metal like sodium and potassium; salts of alkali earth metal like calcium and magnesium; aluminum salt; zinc salt; salts of organic amine like triethylamine, ethanolamine, morpholine, piperidine and dicyclohexylamine and salts of basic amino acid like arginine and lysine. When a basic group exists in the formula, the salts to the basic group include such as salts of inorganic acid like hydrochloric acid, sulfuric acid and phosphoric acid; salts of organic carboxylic acid like oxalic acid, acetic acid, citric acid, malic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, succinate and glutamic acid and salts of organic sulfonic acid like methanesulfonic acid and p- toluenesulfonic acid. The salts can be formed by combining the compounds of general formula (1A) or (1B) and necessary acid or base in the appropriate amount and ratio in a solvent and decomposer. They can be also obtained by the cation or anion exchange from the form of other salts.

[0058] The compounds of general formula (1A) or (1B) of the present invention include solvates such as hydrates and alcohol adducts.

[0059] In the present invention, an inhibitor having the compounds of general formula (1A) or (1B) or salts thereof as an active ingredient can be used as pharmaceutical compositions, in particular, for the treatment of diabetes.

[0060] In the present invention, when the pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives are used as the pharmaceutical compositions, for example, diabetic medicine, they can be given by oral or parenteral administration such as intramuscular, hypodermic and intravenous administrations and suppository. Though the dosage given for the above-mentioned purpose is determined depending on the therapeutic effect, administration method, treatment period, age and weight of the patient, the daily dose for adults is usually 1μg to 10g by oral administration and 0.01μg to 1g by parenteral administration.

[0061] Further, when pyrazole-O-glycoside derivatives and pyrazole-O-glucuronide derivatives of the present invention are prepared as an oral preparation, they can be prepared by ordinary methods after adding diluent bases and, if necessary, binders, disintegrants, lubricants, coloring agents and flavoring agents, in the form of tablets, powders, pills, granules, capsules, suppositories, solutions, dragees, depots or syrups. Diluent bases include such as lactose, cornstarch, sucrose, glucose, sorbit and crystalline cellulose; Binders include such as polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropyl starch and polyvinylpyrrolidone; Disintegrants include such as starch, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogen carbonate, calcium citrate, dextran and pectin; Lubricants include such as magnesium stearate, talc, polyethylene glycols, silica and hardened vegetable oil; Coloring agents include those whose addition to pharmaceutical compounds is permitted; Flavoring agents includes such as cocoa powder, menthol, aromatic acid, mentha oil, borneol and cassia powder. Their tablets and granules may be coated with sugar, gelatin and other coating agents, if necessary.

[0062] When injectable solutions are prepared, they can be prepared by ordinary methods after adding pH adjuster, buffering agents, stabilizing agents and preserving agents, if necessary, in the form of hypodermic, intramuscular, and intravenous injectable solutions.

Examples

[0063] The following Examples will further illustrate the present invention. They are preferred embodiments of the present invention, which by no means limit the invention.

Example 1

Synthesis of 4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O-β -D-glucopyranoside

Process 1

Synthesis of 4'-((4'-methylthiophenyl) methyl)-5'-(trifluoromethyl)-1H-pyrazole-3'-O-(2,3,4,6-O-tetraacetyl)- β -D-glucopyranoside

[0064] 519mg (1.80mmol) of 1,2-dihydro-4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-3H-pyrazole-3-one (prepared by methods described in J. Med. Chem. 1996, 39, 3920-3928), 1.258g (3.06mmol) of 2,3,4,6-O-tetraacetyl-α -D-glucopyranosyl bromide, 112mg (0.36mmol) of benzyl tri-n-butylammonium chloride and 1.244g (9.0mmol) of potassium carbonate were stirred at room temperature for 21 hours after adding 0.1mL of water and 4mL of chloroform. After the reaction was completed, the mixture was controlled by 10% hydrochloric acid to show pH7. After adding 5mL of chloroform and removing water layer, organic layer was washed with 4mL of saturated sodium bicarbonate aqueous solution and 4mL of saturated aqueous sodium chloride solution, respectively. After the product was dried with magnesium sulfate and concentrated, it was purified by silica gel column chromatography (chloroform: methanol = 20:1 (V/V)) to obtain 870mg (1.41mmol) of 4'-((4'-methylthiophenyl) methyl)-5'-(trifluoromethyl)-1H-pyrazole-3'-O-(2,3,4,6-O-tetraacetyl)- β -D-glucopyranoside in the form of pale yellow oily product.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 1.92(3H, s), 2.03(3H, s), 2.05(3H, s), 2.10(3 H, s), 2.45(3H, s), 3.74(2H, s), 4.21(1H, dd, J=2.4, 12.6Hz), 4.28(1H, dd, J=4.2 , 12.6Hz), 5.19-5.28(4H, m), 5.41(1H, d, J=6.3Hz), 7.09(2H, d, J=8.1Hz) 7.16 (2 H, d, J=8.1Hz) ESI-MS(m/z) :619[$(M+H)^+$], 617[$(M-H)^-$]

Process 2

Synthesis of 4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O-β -D-glucopyranoside

[0065] 804mg (1.30mmol) of 4'-((4'-methylthiophenyl) methyl)-5'-(trifluoromethyl)-1H-pyrazole-3'-O-(2,3,4,6-O-tetraacetyl)- β -D-glucopyranoside in the form of pale yellow oil was dissolved in 6mL of ethanol. 0.8mL of 50% aqueous solution of potassium hydroxide was added thereto and the mixture was stirred at room temperature for 10 minutes. After the reaction was completed, the mixture was controlled by 10% hydrochloric acid to show pH7 and further stirred for 24 hours. Crystals thus formed were taken by filtration and washed with 5mL of ethanol. Then the oily product obtained by concentrating the washings was purified by silica gel column chromatography (chloroform: methanol = 10: 1 (V/V)) to obtain 321mg (0.71mmol) of 4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside in the form of white crystals.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 2.43(3H, s), 3.15-3.25(4H, m), 4.39(1H, dd, J=5.3, 12.0Hz), 3.67(1H, d, J=12.0), 3.75 (2H, s), 4.92(1H, br-s), 5.04(1H, br-s), 5.12(1H, br-s), 7.12(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz). ESI-MS(m/z):449[(M-H)$^-$]

Example 2

Synthesis of 4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl-O- β - D-glucopyranoside uronic acid

Process 1

Synthesis of benzyl 4'-[(4'-ethylphenyl) methyl]-5'-(trifluoromethyl)-1H-pyrazole-3'-yl-2,3,4-0-tribenzyl- β -D-glucopyranouronate

[0066] 199mg (0.359mmol) of 2,3,4-tri-0-benzyl-D-glucopyranoside uronic acid benzyl ester (SIGMA), 99mg (0.367mmol) of 1,2-dihydro-4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-3H-pyrazole-3-one (prepared by methods described in J. Med. Chem. 1996, 39, 3920-3928) and 109mg (0.416mmol) of triphenylphosphane were dissolved in 0.5ml of dried THF (not containing stabilizer). 0.18ml (0.40mmol) of 40% toluene solution of diethyl azodicarboxylate was added thereto under cooling with ice and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was directly purified by silica gel chromatography (hexane ~ ethyl acetate: hexane = 1:10 ~ 1:5) and concentrated under reduced pressure to obtain 127mg (0.157mmol) of benzyl 4'-[(4'-ethylphenyl) methyl]-5'-(trifluoromethyl)-1H-pyrazole-3'-yl-2,3,4-0-tribenzyl- β -D-glucopyranouronate in the form of pale yellow oily product.
^{1}H-NMR (300MHz, DMSO-*d6*) δ : 1.12 (3H, t, J=7.8Hz), 2.50 (2H, q, J=7.8H z), 3.64-3.86 (4H, m), 3.90-4.02 (1H, m), 4.05-4.20 (1H, m), 4.40-4.58 (3H, m), 4.65-4.82 (3H, m), 5.10 (1H, d, J=12.1Hz), 5.15(1H, d, J=12.1Hz), 5.20-5.30

(1H, br), 6.90-7.35 (24H, m)

Process 2

Synthesis of 4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl-O- β - D-glucopyranoside uronic acid

[0067] 122mg (0.151mmol) of benzyl 4'-[(4'-ethylphenyl) methyl]-5'-(trifluoromethyl)-1H-pyrazole-3'-yl-2,3,4,-0-tribenzyl- β -D-glucopyranouronate was dissolved in 4ml of ethyl acetate and 4ml of methanol and, in the presence of 204mg of 20%-palladium hydroxide-carbon (50% wet, Aldrich) under hydrogen atmosphere at normal pressures, stirred at room temperature for 8 hours. After filtrating 20%-palladium hydroxide-carbon and washing the mixture with 100ml of dichloromethane: methanol (4:1), the filtrate was evaporated under reduced pressure. The obtained solid substance was suspended in the distilled water and purified by SedPack column (water: methanol = 1:0 ~ 0:1). Then the product was evaporated under reduce pressure at 40°C in the bath or lower to obtain 22mg (0.050mmol) of 4-[(4-ethylphenyl) methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl- β - D-glucopyranoside uronic acid in the form of amorphous white solid substance.
^{1}H-NMR (300MHz, DMSO-*d6*) δ : 1.19 (3H, t, J=7.5Hz), 2.58 (2H, q, J=7.5H z), 3.35-3.51 (2H, m), 3.52-3.65 (1H, m), 3.70-3.90 (3H, m), 5.00-5.20 (1H, br), 7.06 (2H, d, J=8.4Hz), 7.09 (2H, d, J=8.4Hz) ESI-MS(m/z) 445[$(M-H)^+$], 447[$(M+H)^+$]

Example 3

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O- β -D-glucopyranoside

Process 1

Synthesis of 4-[(4-ethylphenyl) methyl]-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole

[0068] 4.76g (17.6mmol) of 1,2-dihydro-4-[(4-ethylphenyl) methyl]-5-trifluoromethyl-3H-pyrazole-3-one (prepared by methods described in J. Med. Chem. 1996, 39, 3920-3928) and 1.57g (23.1mmol) of imidazole were dissolved in 20ml of dimethylformamide. 2.98g (19.8mmol) of t-butyldimethylsilylchloride was added thereto and the mixture was stirred at room temperature for 30 minutes. After adding 100ml of water, the mixture was extracted with a mixed solution of ethyl acetate-hexane (2:1) three times. The organic layer was washed with water, dried over sodium sulfate and concentrated to obtain 6.9g of the intended product (17.9mmol, quantitative).
^{1}H-NMR(300MHz, $CDCl_3$) δ : 0.21 (6H, s), 0.93 (9H, s), 1.19 (3H, t, J=7.6 Hz), 2.59 (2H, q, J= 7.6Hz), 3.74 (2H, s), 7.09 (4H, pseudo ABq) ESI-MS(m/ z) 269 [$(M-TBS)^-$]

Process 2

Synthesis of 4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole

[0069] 0.39g (1.0mmol) of 4-[(4-ethylphenyl) methyl]-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole, 0.30g (1.1mmol) of triphenylphosphane and 0.14ml (1.4mmol) of benzyl alcohol were dissolved in 2.0ml of anhydrous tetrahydrofuran and stirred at room temperature. 0.50ml (1.1mmol) of 40% toluene solution of diethyl azodicarboxylate was slowly added thereto and, 20 minutes later, the mixture was concentrated. Then 1ml of hexane was added, and formed sediments were taken by filtration, concentrated and purified by silica gel column (hexane→5% ethyl acetate/ hexane) to obtain 0.40g (0.83mmol) of the intended product (83%).
^{1}H-NMR(300MHz, $CDCl_3$) δ : 0.22 (6H, s), 0.92 (9H, s), 1.20 (3H, t, J=7.5 Hz), 2.59 (2H, q, J= 7.5Hz), 3.74 (2H, s), 5.19 (2H, s), 7.06 (4H, pseudo ABq) , 7.11-7.33 (5H, m)

Process 3

Synthesis of 4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole

[0070] 0.40g (0.83mmol) of 4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole was dissolved in 2ml of tetrahydrofuran and 0.5ml of methanol and 1ml of 1M-HCl aqueous solution was added thereto and the mixture was stirred at room temperature for 7 hours. After adding 5ml of water, the mixture was extracted with 5ml of ethyl acetate three times. The product was dried over sodium sulfuric anhydride, concentrated and purified by silica gel column (hexane→ 10% ethyl acetate/ hexane) to obtain 0.27g (0.74mmol) of the intended product (89%).

^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.21 (3H, t, J=7.6 Hz), 2.61 (2H, q, J=7.6 Hz) , 3.77 (2H, s), 5.18 (2H, s), 7.07-7.31 (9H, m) ESI-MS(m/z) [361 $(M+H)^+$], [3 59 $(M-H)^-$]

Process 4

Synthesis of 4'-[(4-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside

[0071] 1mL of water and 10mL of chloroform were added to 0.22g (0.62mmol) of 4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole, 0.39g (0.94mmol) of 2,3,4,6-O-tetraacetyl- α -D-glucopyranosyl bromide, 0.055g (0.18mmol) of benzyl tri-n-butylammonium chloride, 0.79g (5.7mmol) of potassium carbonate and the mixture was stirred at room temperature overnight. About 0.1g of benzyl tri-n-butylammonium chloride was added thereto and the mixture was further stirred overnight. The organic layer was purified by silica gel column chromatography (ethyl acetate: hexane = 10:1) to obtain 0.39 of roughly purified substance containing the intended product mainly and the further reaction proceeded.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.19 (3H, t, J=7.6 Hz), 1.86 (3H, s), 2.015 (3 H, s), 2.019 (3H,s), 2.03 (3H, s), 2.58 (2H, q, J=7.6 Hz), 3.74 (2H, s), 3.81 (1 H, ddd, J=9.5, 4.2, 2.3 Hz), 4.08 (1H, dd, J=12.5, 2.3 Hz), 4.27 (1H, dd, J=12 .5, 4.2 Hz), 5.16-5.28 (3H, m), 5.24 (2H, s), 5.58-5.63 (1H, m), 7.05 (4H, s), 7.16-7.35 (5H, m) ESI-MS(m/z) [691 $(M+H)^+$]

Process 5

Synthesis of 4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0072] 0.28g of roughly purified substance of 4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside was dissolved in 5ml of ethanol and 5ml of 4N NaOH aqueous solution was added thereto and the mixture was stirred at room temperature. 1 hour later, 50ml of water was added and the mixture was extracted with ethyl acetate five times. Then the product was concentrated and purified by silica gel column (dichloromethane→10% methanol/ dichloromethane) to obtain 0.11g (0.21mmol) of the intended product.
^{1}H-NMR(300MHz, CD3OD) δ : 1.19 (3H, t, J=7.6 Hz), 2.58 (2H, q, J=7.6 H z), 3.34-3.46 (4H, m), 3.68 (1H, dd, J=12.0, 4.7 Hz), 3.81 (1H, dd, J=12.0, 2. 1 Hz), 3.83 (2H, s), 5.32 (2H, s), 5.34-5.37 (1H, m), 7.07 (4H, s), 7.10-7.12 (2H, m), 7.25-7.33 (3H, m)

Example 4

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0073] 0.11g (0.21mmol) of 4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O- β -D-glucopyranoside was dissolved in 1.5ml of pyridine and cooled in the ice bath. 0.020ml (0.26mmol) of methyl chlorocarbonate was added thereto and the temperature of the mixture was raised up to room temperature in 0.5 hour. 0.020ml (0.26mmol) of methyl chlorocarbonate was further added 2 hours later and 19 hours later, then the mixture was stirred at room temperature for 6 hours. 5ml of ethyl acetate, 10ml of 1M HCl aqueous solution and 20ml of water were added thereto and the mixture was extracted with ethyl acetate. Then the product was dried, concentrated and purified by silica gel column (ethyl acetate) to obtain 0.059g (0.10mmol) of the intended product (47%).
^{1}H-NMR(300MHz, CDCl3) δ : 1.18 (3H, t, J=7.6 Hz), 2.57 (2H, q, J=7.6 Hz), 3.48-3.60 (4H, m), 3.70 (3H, s), 3.74 (1H, d, J=15.8 Hz), 3.82 (1H, d, J=1 5.8 Hz), 4.34 (2H, s), 5.22 (1H, d, J=4.4 Hz), 5.23 (2H, s), 7.07 (4H, s), 7.12 (2H, d, J=6.4 Hz), 7.21-7.32 (3H, m) ESI-MS(m/z) [581 $(M+H)^+$], [579 $(M-H)^-$]

Example 5

Synthesis of 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside

Process 1

Synthesis of 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole

[0074] The intended product was obtained in the same manner as shown in Process 2 of Example 3, by using 4-methoxy benzyl bromide instead of benzyl bromide.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 0.22 (6H, s), 0.93 (9H, s), 1.19 (3H, t, J=7.6 Hz), 2.58 (2H, q, J=.6 Hz), 3.72 (2H, s), 3.78 (3H, s), 5.14 (2H, s), 6.83 (2H, d, J=8.8 Hz), 7.07 (4H, pseudo ABq), 7.16 (2H, d, J=8.8 Hz)

Process 2

Synthesis of 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-(trifluoromethyl)-1H-pyrazole

[0075] The intended product was obtained (82%) from 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-(trifluoromethyl)-3-O-t-butyldimethylsilyl-1H-pyrazole in the same manner as shown in Process 3 of Example 3
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.21 (3H, t, J=7.5 Hz), 2.60 (2H, q, J=7.5 Hz) , 3.77 (5H, s), 5.10 (2H, s), 6.81-6.84 (2H, m), 7.07-7.19 (6H, m) ESI-MS(m/z) [391 $(M+H)^+$], [389 $(M-H)^-$]

Process 3

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-[(4-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside

[0076] The roughly purified product of the intended product was obtained from 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-(trifluoromethyl)-1H-pyrazole in the same manner as shown in Process 4 of Example 3.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.19 (3H, t, J=7.6 Hz), 1.86 (3H, s), 2.07 (3H, s), 2.11 (6H, s), 2.58 (2H, q, J = 7.6 Hz), 3.73 (2H, s), 3.75-3.84 (1H, m), 4 .24-4.30 (1H, m), 5.16 (2H, s), 5.19-5.28 (3H, m), 5.56-5.60 (1H, m), 6.75 (2H, d, J=8.8 Hz), 7.05 (4H, s), 7.15 (2H, d, J=8.8 Hz)
ESI-MS(m/z) [721 $(M+H)^+$]

Process 4

Synthesis of 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0077] The intended product was obtained (91% in 2 steps) from 4'-[(4'-ethylphenyl) methyl]-1'-[(4-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside in the same manner as shown in Process 5 of Example 3.
^{1}H-NMR(300MHz, CD3OD) δ : 1.19 (3H, t, J=7.6 Hz), 2.57 (2H, q, J=7.6 H z), 3.36-3.44 (4H, m), 3.66-3.82 (2H, m), 3.76 (3H, s), 3.82 (2H, s), 5.24 (2 H, s), 5.33-5.36 (1H, m), 6.86 (2H, d, J=8.5 Hz), 7.07 (4H, s), 7.12 (2H, d, J =8.5 Hz)
ESI-MS(m/z) [553 $(M+H)^+$], [551 $(M-H)^-$]

Example 6

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-[(4'-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0078] 0.18g (0.32mmol) of 4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside was dissolved in 2ml of 2,4,6-collidine and cooled down to -50 °C. 0.035ml (0.45mmol) of methyl chlorocarbonate was added thereto and the temperature of the mixture was raised up to room temperature in 1 hour. 27 hours later, 20ml of ethyl acetate and 20ml of 1M HCl aqueous solution were added thereto and the mixture was extracted with ethyl acetate. Then the product was dried, concentrated and purified by silica gel column (hex-

ane→ethyl acetate) to obtain 0.12g (0.20mmol) of the intended product (62%).
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.21 (3H, t, J=7.6 Hz), 2.26 (1H, d, J=2.3 Hz) , 2.61 (2H, q, J=7.6 Hz), 2.69 (1H, s), 2.86 (1H, s), 3.45-3.61 (4H, m), 3.73 (1H, d, J=15.2 Hz), 3.80 (3H, s), 3.80 (3H, s), 3.88 (1H, d, J=15.2 Hz), 4.37 (1 H, d, J=12.3 Hz), 4.49 (1H, dd, J=12.3, 3.0 Hz), 5.19 (2H, s), 5.20 (1H, d, J= 7.6 Hz), 6.86 (2H, d, J=8.5 Hz), 7.10 (4H, s), 7.16 (2H, d, J=8.5 Hz)

Example 7

Synthesis of 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside

Process 1

Synthesis of 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole

[0079] 0.079g (0.21mmol) of 4-[(4-ethylphenyl) methyl]-5-trifluoromethyl-3-O-t-butyldimethylsilyl-1H-pyrazole, 0.049g (0.40mmol) of phenylboronic acid and 0.057g (0.32mmol) of copper acetate anhydride were dissolved in 5ml of dried dichloromethane. 0.15g of molecular sieves 4A powder and 0.032ml (0.40mmol) of pyridine were added thereto and the mixture was stirred at room temperature overnight. Then the reaction mixture was purified by silica gel column (hexane→ hexane: dichloromethane = 5:1～3:1) and the main product was separated to obtain 0.074g (0.16mmol) of the intended product (80%).
^{1}H-NMR(300MHz, $CDCl_3$) δ : 0.27 (6H, s), 0.96 (9H, s), 1.21 (3H, t, J=7.6H z), 2.61 (2H, q, J=7.6Hz), 3.84 (2H, s), 7.11 (2H, J=8.3Hz), 7.18 (2H, J=8.3Hz), 7.35-7.45 (5H, m) ESI-MS(m/z) [461 $(M+H)^+$], [459 $(M-H)^-$]

Process 2

Synthesis of 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole

[0080] The intended product was obtained (95%) from 4-[(4-ethylphenyl) methyl]-1-phenyl-5-(trifluoromethyl)-3-O-t-butyldimethylsilyl-1H-pyrazole in the same manner as shown in Process 3 of Example 3.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.22 (3H, t, J=7.6Hz), 2.62 (2H, q, J=7.6Hz), 3.81 (2H, s), 7.10 (2H, d, J=8.1Hz), 7.17 (2H, d, J=8.1Hz), 7.35-7.50 (5H, m) , 10.40-10.80 (1H, br-s) ESI-MS(m/z)
[347 $(M+H)^+$], [345 (M-H)-]

Process 3

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside

[0081] The roughly purified product of the intended product was obtained from 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole in the same manner as shown in Process 4 of Example 3.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.21 (3H, t, J=7.6Hz), 1.90 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.61 (2H, q, J=7.6Hz), 3.80-3.90 (2H, s and 1 H, m), 4.10-4.30 (2H, m), 5.15-5.36 (3H, m), 5.68 (1H, d, J=7.5Hz), 7.10 (2 H, d, J=8.3Hz), 7.15 (2H, d, J=8.3Hz), 7.38-7.47 (5H, m)
ESI-MS(m/z) [677 $(M+H)^+$]

Process 4

Synthesis of 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0082] The intended product was obtained (84% in 2 steps) from the roughly purified product of 4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside in the same manner as shown in Process 5 of Example 3.
^{1}H-NMR(300MHz, DMSO—d_6) δ : 1.19 (3H, t, J=7.6Hz), 2.60 (2H, q, J=7.6 Hz), 3.15-3.35 (4H, m), 3.45-3.55 (1H, m), 3.69 (1H, dd, J=11.4, 5.7Hz), 3.8 5 (1H, d, J=15.6Hz), 3.92 (1H, d, J=15.6Hz), 4.55 (1H, t, J=5.7Hz), 5.03 (1H, d, J=4.5Hz), 5.13 (1H, d, J=3.9Hz), 5.35 (1H, d, J=7.5Hz), 5.41 (1H, d, J=4.5 Hz), 7.17 (2H, d, J=8.3Hz), 7.22 (2H, d, J=8.3Hz), 7.47-7.62 (5H, m)
ESI-MS(m/z) [509 $(M+H)^+$], [507 $(M-H)^-$]

Example 8

Synthesis of 4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0083] The intended product was obtained (71%) from 4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside in the same manner as shown in Example 4.
^{1}H-NMR(300MHz, $CDCl_3$) δ : 1.22 (3H, t, J=7.6Hz), 2.18 (1H, br), 2.62 (2H, q, J=7.6Hz), 2.72 (1H, br), 2.89 (1H, br), 3.45-3.63 (4H, m), 3.78 (3H, s), 3. 81 (1H, d, J=15.6Hz), 3.98 (1H, d, J=15.6Hz), 4.37 (1H, dd, 12.0, 1.7Hz), 4.49 (1H, dd, 12.0, 3.6Hz), 5.32 (1H, d, J=7.2Hz), 7.14 (2H, d, J=8.3Hz), 7.19 (2H , d, J=8.3Hz), 7.39-7.47 (5H, m) ES]-MS(m/z) [567 (M+H)+], [565 (M-H)-]

Example 9

Synthesis of 4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

Process 1

Synthesis of ethyl 2-[(3-fluoro-4-methoxy) benzyl]-3-oxobutyrate

[0084] 1.69g (13.0mmol) of ethyl acetoacetate and 9.6g (65mmol) of sodium iodide were dissolved in 100ml of acetonitrile and cooled down to 0°C. 8.2ml (65mmol) of trimethylsilylchloride was slowly added thereto and 10 minutes later, 2.0g (13.0mmol) of 3-fluoro-4-methoxybenzaldehyde was added in three times. 10 minutes later, the temperature of the mixture was raised up to room temperature and the mixture was continuously stirred. 6 hours later, the mixture was moved into the 60°C bath and stirred overnight. After the reaction mixture was cooled down, 250ml of water, 250ml of ethyl acetate and 50ml of saturated aqueous sodium chloride solution were added thereto, and ethyl acetate layer was extracted. The obtained organic layer was washed with saturated sodium sulfite aqueous solution and dried over anhydrous magnesium sulfate. Then the product was concentrated and purified by silica gel column chromatography (EtOAc-Hex; 1:4) to obtain 2.54g (9.5mmol) of the intended product (yield 73%).
^{1}H-NMR (300MHz,$CDCl_3$) δ :6.82-6.96 (3H, m), 4.12-4.20 (2H, m), 3.86 (3H, s) , 3.71 (1H, t, J=7.8), 3.08 (2H, d, J=8.1), 2.20 (3H, s), 1.23 (3H, t, J=7.2).

Process 2

Synthesis of 1,2-dihydro-4-[(3-fluoro-methoxyphenyl) methyl]-5-methyl-3H-pyrazole-3-one

[0085] 2.54g (9.5mmol) of ethyl 2-[(3-fluoro-4-methoxy) benzyl]-3-oxobutyrate was dissolved in 50ml of toluene. 0.72g (14.2mmol) of hydrated hydrazine was added thereto and the mixture was stirred at 100°C overnight. After the reaction mixture was cooled down, the formed white solid was filtrated and dried by a vacuum pump to obtain 1.86g (7.9mmol) of the intended product (yield 83%).
^{1}H-NMR (300MHz, DMSO-*d6*) δ:7.00 (1H, t, J=8.4), 6.86-6.94 (2H, m), 3.75 (3H, s), 3.46 (2H, s), 1.98 (3H, s). ESI-MS (m/z) : 237[$(M+H)^+$], 235[$(M-H)^-$].

Process 3

Synthesis of 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0086] 2.3g (4.2mmol) of 2,3,4,6-tetra-0-benzyl-D-glucopyranoside, 1.0g (4.2mmol) of 1,2-dihydro-4-[(3-fluoro-4-methoxyphenyl) methyl]-5-methyl-3H-pyrazole-3-one and 1.1g (4.2mmol) of triphenylphophane were dissolved in 40ml of dried THF (not containing stabilizer). 1.9ml(4.2mmol) of 40% toluene solution of diethyl azodicarboxylate was added thereto under cooling with ice and the mixture was stirred at room temperature overnight. After the reaction mixture was concentrated, the product was directly purified by silica gel column chromatography (hexane ~ ethyl acetate: hexane = 2:3) and concentrated under reduced pressure to obtain 2.2g (2.9mmol) of the intended product (yield 70%).
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.10-7.32 (20H, m), 6.78-6.92 (2H, m), 6.67 (1H, t ,J=8.1), 5.51 (1H, d, J=7.5), 4.46-4.92 (10H, m), 3.60-3.76 (6H, m), 3.71 (3 H, s), 2.07 (3H, s). ESI-MS(m/z) : 759[$(M+H)^+$], 757[$(M-H)^-$].

Process 4

Synthesis of 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0087] 2.2g (2.9mmol) of 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside was dissolved in 44ml of dimethylformamide. 9.6g (29.5mmol) of cesium carbonate and 2.5g (14.8mmol) of isopropyl iodide were added thereto and the mixture was stirred at room temperature overnight.

[0088] 200ml of water, 50ml of saturated aqueous sodium chloride solution and 300ml of dichloromethane were added and the organic layer was extracted, dried over anhydrous sodium sulfate and concentrated. The product was purified by silica gel column chromatography (hexane ~ ethyl acetate: hexane = 1:3) and concentrated under reduced pressure to obtain 1.7g (2.2mmol) of the intended product (yield 74%).

^{1}H-NMR (300MHz, $CDCl_3$) δ:7.12-7.32 (20H, m), 6.80-6.92 (2H, m), 6.68 (1H, t, J=8.4), 5.47 (1H, d, J=7.2), 4.74-4.94 (5H, m), 4.44-4.64 (5H, m), 4.24-4.32 (1H, m), 3.73 (3H, s), 3.60-3.72 (6H, m), 2.06 (3H, s), 1.38 (3H, t, J=7.5). ESI-MS(m/z) : 801[$(M+H)^+$].

Process 5

Synthesis of 4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0089] 1.7g (2.2mmol) of 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside was dissolved in 70ml of ethanol. 1.0g of 20% palladium hydroxide - carbon was added thereto and the mixture was stirred for 2 hours under hydrogen atmosphere. The reaction mixture was filtrated by a filter cell and the filtrate was concentrated and purified by silica gel chromatography (15% methanol: dichloromethane) and then concentrated under reduced pressure to obtain 828mg (1.9mmol) of the intended product (yield 88%).

^{1}H-NMR (300MHz, DMSO-*d6*) δ :6.92-7.04 (3H, m), 5.20 (1H, d, J=4.5), 5.11 (1H, d, J=7.2), 5.02 (1H, d, J=3.6), 4.93 (1H, d, J=4.5), 4.41 (1H, t, J=5.7), 4. 28-4.40 (1H, m), 3.77 (3H, s), 3.56-3.66 (1H, m), 3.42-3.52 (1H, m), 3.08-3.24 (4H, m), 2.07 (3H, s), 1.24-1.30 (3H, m). ESI-MS(m/z) : [441$(M+H)^+$].

Example 10

Synthesis of 4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0090] 820mg (1.9mmol) of 4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside was dissolved in 8ml of collidine and cooled down to 0°C. 10 minutes later, 0.22ml of methyl chlorocarbonate was added thereto and the mixture was stirred for 7 hours, neutralized with 2N HCl and extracted with ethyl acetate. Then the organic layer was dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography (ethyl acetate) and then concentrated under reduced pressure to obtain 303mg (0.61mmol) of the intended product (yield 33%).

^{1}H-NMR (300MHz, $CDCl_3$) δ :6.80-6.92 (3H, m), 5.02 (1H, d, J=8.1), 4.40 (2H, s), 4.22-4.34 (1H, m), 3.85 (3H, s), 3.78 (3H, s), 3.44-3.66 (6H, m),2.08 (3H, s), 1.38 (6H, d, J=6.6) . ESI-MS(m/z) : [499$(M+H)^+$].

Example 11

Synthesis of 4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

Process 1

Synthesis of ethyl 2-[(2-fluoro-4-methoxy) benzyl]-3-oxobutyrate

[0091] 3.4g (12.7mmol) of the intended product was obtained (yield 65%) from 3.0g of 2-fluoro-4-methoxybenzaldehyde in the same manner as shown in Process 1 of Example 9.

^{1}H-NMR (300MHz, $CDCl_3$) δ: 7.07 (1H, t, J=8.7), 6.40-6.62 (2H, m), 4.10-4.20 (2H, m), 3.79 (1H, t, J=7.8), 3.77 (3H, s), 3.04-3.18 (2H, m), 2.21 (3H, s), 1. 21 (3H, t, J=7.2).

Process 2

Synthesis of 1,2-dihydro-4-[(2-fluoro-4-methoxylphenyl) methyl]-5-methyl-3H-pyrazole-3-one

[0092] 2.46g (10.4mmol) of the intended product was obtained (yield 83%) from 3.4g of ethyl 2-[(2-fluoro-4-methoxy) benzyl]-3-oxobutyrate in the same manner as shown in Process 2 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ : 7.02 (1H, t, J=8.7), 6.72 (1H, dd, J=2.4, 12.0), 6.66 (1H, d, J=2.7, 8.4), 3.71 (3H, s), 3.47 (2H, s), 1.99 (3H, s) ESI-MS(m/z) : 237[$(M+H)^+$], 235[$(M-H)^-$].

Process 3

Synthesis of 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0093] 2.6g (3.46mmol) of the intended product was obtained (yield 82%) from 1.0g (4.2mmol) of 1,2-dihydro-4-[(2-fluoro-4-methoxyphenyl) methyl]-5-methyl-3H-pyrazole-3-one in the same manner as shown in Process 3 of Example 9.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 7.12-7.32 (20H, m), 6.99 (1H, t, J=9.0), 6.50 (1H, dd, J=2.4, 11.7), 6.42 (1H, dd, J=2.7, 8.4), 5.54 (1H,d, J=7.2), 4.44-4.92 (8H, m), 3.60-3.76 (8H, m), 3.62 (3H, s), 2.09 (3H, s) ESI-MS(m/z) : 759[$(M+H)^+$], 757[$(M-H)^-$].

Process 4

Synthesis of 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0094] 157mg (0.19mmol) of the intended product was obtained (yield 70%) from 212mg (0.28mmol) of 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside in the same manner as shown in Process 4 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.14-7.30 (20H, m), 6.99 (1H, t, J=8.7), 6.49 (1H , dd, J=2.4, 11.7), 6.41 (1H, dd, J=2.4, 8.7), 5.50 (1H, d, J=7.5), 4.74-4.96 (5H , m), 4.46-4.66 (5H, m), 4.22-4.32 (1H, m), 3.64 (3H, s), 3.60-3.74 (6H, m),2.08 (3H, s), 1.37 (6H, t, J=6.6). ESI-MS(m/z) : 801[$(M+H)^+$].

Process 5

Synthesis of 4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0095] 80mg (0.18mmol) of the intended product was obtained (yield 97%) from 150mg (0.19mmol) of 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside in the same manner as shown in Process 5 of Example 9.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 7.09 (1H, t, J=9.0), 6.73 (1H, dd, J=2.7, 12. 3), 6.66 (1H, dd, J=2.7, 8.7), 5.18 (1H, d, J=4.8), 5.11 (1H, d, J=7.5), 5.01 (1 H, d, J=4.2), 4.91 (1H, d, J=4.2), 4.42 (1H, t, J=6.0), 4.30-4.38 (1H, m), 3.72 (3H, s) , 3.53 (2H, s), 3.42-3.66 (2H, m), 3.06-3.24 (4H, m),2.07 (3H, s), 1.28 (3H, d, J=2.7), 1.26 (3H, d, J=2.7). ESI-MS (m/z) : 441[$(M+H)^+$], 439[$(M-H)^-$].

Example 12

Synthesis of 4'-[(2'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0096] 380mg (0.76mmol) of the intended product was obtained (yield 31%) from 1.1g (2.42mmol) of 4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β -D-glucopyranoside.
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.08 (1H, t, J=8.4), 6.52-6.62 (2H, m), 5.02 (1H, d, J=7.8), 4.64 (1H, brs), 4.40 (2H, d, J=2.4), 4.24-4.33 (1H, m), 3.77 (3H, s), 3.75 (3H, s), 3.59 (3H, s), 3.10-3.66 (6H, m), 1.38 (3H, s), 1.35 (3H, s)

Example 13

Synthesis of 4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

Process 1

Synthesis of ethyl 2-[(3-fluoro-4-methyl) benzyl]-3-oxobutyrate

[0097] 4.5g (17.9mmol) of the intended product was obtained (yield 82%) from 3.0g (21.7mmol) of 3-fluoro-4-methylbenzaldehyde in the same manner as shown in Process 1 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.06 (1H, t, J=8.1), 6.78-6.88 (2H, m), 4.15 (2H, q, J=6.9), 3.73 (1H, t, J=7.8), 3.10 (1H, d, J=7.8), 2.22 (3H, s), 2.19 (3H, s), 1.22 (3H, t, J=6.9).

Process 2

Synthesis of 1,2-dihydro-4-[(3-fluoro-4-methylphenyl) methyl]-5-methyl-3H-pyrazole-3-one

[0098] 2.3g (10.5mmol) of the intended product was obtained (yield 93%) from 2.84g (11.3mmol) of ethyl 2-[(3-fluoro-4-methyl) benzyl]-3-oxobutyrate in the same manner as shown in Process 2 of Example 9.
^{1}H-NMR (300MHz, DMSO-*d6*) δ :7.11 (1H, d, J=8.4), 6.81-6.89 (2H, m), 3.49 (2H, s), 2.13 (3H, s), 1.98 (3H, s). ESI-MS (m/z) : 221[$(M+H)^+$]

Process 3

Synthesis of 4'-[(3'-fluoro-4'-methylphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside

[0099] 2.1g (5.0mmol) of 2,3,4,6-0-tetraacetyl- α -D-glucopyranosyl bromide, 1.1g (5.0mmol) of 1,2-dihydro-4-[(3-fluoro-4-methylphenyl) methyl]-5-methyl-3H-pyrazole-3-one and 1.38g (5mmol) of silver carbonate were dissolved in 50ml of dried THF (not containing stabilizer) and the mixture was stirred under dark at 65°C overnight. The reaction mixture was filtrated with a filter cell and dichloromethane was added thereto. After washing the mixture with water, the organic layer was dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography (hexane ~ ethyl acetate: hexane = 1:3) and then concentrated under reduced pressure to obtain 1.1g (2.0mmol) of the intended product (yield 40%).
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.03 (1H, t, J=7.5), 6.82 (1H, dd, J=1.2, 7.8), 6. 74 (1H, dd, J=1.5, 10.8), 5.59 (1H, d, J=8.1), 5.16-5.30 (3H, m), 4.31 (1H,dd, J=3.9, 12.3), 4.12 (1H, dd, J=2.1, 12.3), 3.82-3.88 (1H, m), 3.63 (1H, d, J=15.9), 3.54 (1H, d, J=15.9), 2.20 (3H, d, J=1.5), 2.11 (3H, s), 2.06 (3H, s), 2.03 (3H, s), 2.02 (3H, s), 1.91 (3H, s). ESI-MS (m/z) : 551[$(M+H)^+$], 549[$(M-H)^-$].

Process 4

Synthesis of 4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside

[0100] 290mg (0.53mmol) of 4'-[(3'-fluoro-4'-methylphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside was dissolved in 6ml of dimethylformaldehyde. 1.7g (5.2mmol) of cesium carbonate and 447mg (2.6mmol) of isopropyl iodide were added thereto and the mixture was stirred at room temperature over night. After adding water, saturated aqueous sodium chloride solution and dichloromethane, the organic layer was extracted by a separating funnel, dried over anhydrous sodium sulfate and concentrated. The product was purified by silica gel chromatography (hexane ~ ethyl acetate: hexane = 1:3) and then concentrated under reduced pressure to obtain 165mg (0.28mmol) of the intended product (yield 53%).
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.02 (1H, t, J=7.8), 6.82 (1H, d, J=7.8), 6.74 (1 H, d, J=10.8), 5.79 (1H, d, J=8.1), 5.12-5.34 (3H, m), 4.18-4.32 (2H, m), 4.06-4.16 (1H, m), 3.78-3.88 (1H, m), 3.48-3.64 (2H, m), 2.19 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 2.02 (3H, s), 1.93 (3H, s). ESI-MS(m/z) : 593[M^+].

Process 5

Synthesis of 4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0101] 56mg (0.09mmol) of 4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetraacetyl)- β -D-glucopyranoside was dissolved in 0.2ml of methanol and 0.4ml of tetrahydrofuran. 0.38ml of 1N LiOH was added at 0°C thereto and the mixture was stirred for 1 hour. After adding water and ethyl acetate, the organic layer was extracted, dried, concentrated and purified by silica gel chromatography (15% methanol: dichloromethane) and then concentrated under reduced pressure to obtain 34mg (0.08mmol) of the intended product (yield 85%).
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 7.11 (1H, t, J=8.4), 5.19 (1H, d, J=4.8), 5.0 9 (1H, d, J=7.5), 4.99 (1H, d, J=3.9), 4.91 (1H, d, J=4.2), 4.41 (1H, t, J=5.7), 4.28-4.38 (1H, m), 3.56 (2H, m), 3.54-3.64 (1H, m), 3.40-3.50 (1H, m),3.06-3. 24 (4H, m), 2.13 (3H, s), 2.05 (3H, s), 1.26 (3H, d, J=3.0), 1.24 (3H, d, J=3.0). ESI-MS(m/z) : 425[(M+H)$^+$], 423[(M-H)$^-$].

Example 14

Synthesis of 4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

[0102] 283mg (0.59mmol) of the intended product was obtained (yield 75%) from 334mg (0.787mmol) of 4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside in the same manner as shown in Example 12.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 1.26(3H, d, J=6.3Hz), 1.28(3H, d, J=6.3Hz), 2.07(3H, s), 2.15(3H, s), 3.09-3.41(4H, m), 3.56(2H, s), 4.10(1H, dd, J=6.0, 11. 4Hz), 4.29(1H, dd, J=1.8, 11.7Hz), 4.34(1H, m), 5.10(1H, d, J=7.8Hz), 5.13 (1H, d, J=5.1Hz) 5.24(1H, d, J=5.1Hz), 5.31(1H, d, J=5.1Hz) 6.89-7.13(3H, m). E SI-MS(m/z) :483[M+H]$^+$ 481[(M-H)$^-$]

Example 15

Synthesis of 4-[(4-ethylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O- β - D-glucopyranoside

Process 1

Synthesis of ethyl 2-(4-ethylbenzyl)-3-oxobutyrate

[0103] 3.9g (15.7mmol) of the intended product was obtained (yield 70%) from 3.0g of 4-ethylbenzaldehyde in the same manner as shown in Process 1 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ :4.15 (2H, q, J=7.2),3.76 (1H, t, J=7.5), 3.12 (2H, d, J=8.1), 2.60 (2H, q, J=7.8), 2.19 (3H, s), 1.21 (6H, t, J=7.2)

Process 2

Synthesis of 1,2-dihydro-4-[(4-ethylphenyl) methyl]-5-methyl-3H-pyrazole-3-one

[0104] 3.1g (14.3mmol) of the intended product was obtained (yield 91%) from 3.9g of ethyl 2-(4-ethylbenzyl)-3-oxobutyrate in the same manner as shown in Process 2 of Example 9.
^{1}H-NMR (300MHz, DMSO-*d6*) δ : 7.06 (4H, s),3.49 (2H, s), 2.52 (2H, q, J=7.8), 1.99 (3H, s), 1.33 (3H, t, J=7.5) ESI-MS (m/z) : 217[(M+H)$^+$], 215[(M-H)$^-$].

Process 3

Synthesis of 4'-[(4-ethylphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0105] 2.3g (3.1mmol) of the intended product was obtained (yield 62%) from 1.0g (4.6mmol) of 1,2-dihydro-4-[(4-ethylphenyl) methyl]-5-methyl-3H-pyrazole-3-one in the same manner as shown in Process 3 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.10-7.34 (20H, m), 7.07 (2H, d, J=8.4), 6.97 (2H, d, J=8.4), 5.23 (1H, d, J=6.9), 4.44-5.00 (8H, m), 3.56-3.80 (8H, m), 2.50 (2H, q, J=7.5), 2.08 (3H, s), 1.13 (3H, t, J=7.5): ESI-MS(m/z) : 739[(M+H)$^+$], 737[(M-H)$^-$].

Process 4

Synthesis of 4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside

[0106] 1.6g (2.0mmol) of the intended product was obtained (yield 79%) from 1.9g (2.6mmol) of 4'-[(4-ethylphenyl) methyl]-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside in the same manner as shown in Process 4 of Example 9.
^{1}H-NMR (300MHz, $CDCl_3$) δ :7.14-7.38 (20H, m), 7.07 (2H, d, J=8.1), 6.97 (2H, d, J=8.1), 5.47 (1H ,d ,J=7.5), 4.20-5.00 (9H, m), 3.60-3.76 (8H, m), 2.52 (2H, q J=7.8), 2.07 (3H, s), 1.37 (6H, t, J=6.9), 1.14 (3H, t, J=8.1): 781[$(M+H)^+$].

Process 5

Synthesis of 4-[(4-ethylphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β - D-glucopyranoside

[0107] 743mg (1.8mmol) of the intended product was obtained (yield 87%) from 1.6g (2.0mmol) of 4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(2,3,4,6-tetrabenzyl)- β -D-glucopyranoside in the same manner as shown in Process 5 of Example 9.
^{1}H-NMR (300MHz, DMSO-*d6*) δ: 7.09 (2H, d, J-7.8), 7.03 (2H, d, J=7.8), 5.18 (1H,brd, J=4.5), 5.11 (1H, d, J=6.9), 4.84-5.02 (2H, m), 4.26-4.44 (3H, m), 3.40-3.64 (3H, m), 3.04-3.26 (4H, m), 2.51 (2H, q, J=7.5), 2.06 (3H, s), 1.25 (6H, d, J=6.6), 1.14 (3H, t, J=5.7) : 421[$(M+H)^+$], 419[$(M-H)^-$].

Example 16

Synthesis of 4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside

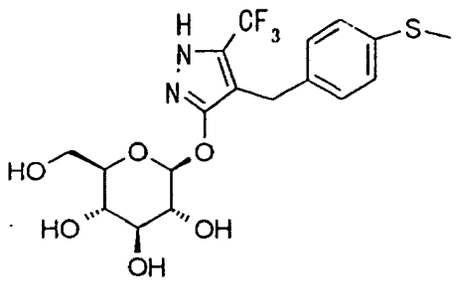
[0108] 570mg (1.2mmol) of the intended product was obtained (yield 71%) from 702mg (1.67mmol) of 4-[(4-ethylphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β -D-glucopyranoside in the same manner as shown in Example 10.
^{1}H-NMR (300MHz, $CDCl_3$) δ : 7.08 (4H, s), 4.99 (1H, d, J=7.5), 4.24-4.48 (4H, m), 3.77 (3H, s), 3.44-3.68 (6H, m), 2.94-3.16 (2H, m), 2.58 (2H, q, J=7.8), 2.09 (3H, s), 1.36 (6H, d, J=6.6), 1.20 (3H, t, J=7.8) ESI-MS(m/z) : 479[$(M+H)^+$], 477[$(M-H)^-$].

Referential Example 1 (Example 35 of WO01/16147)

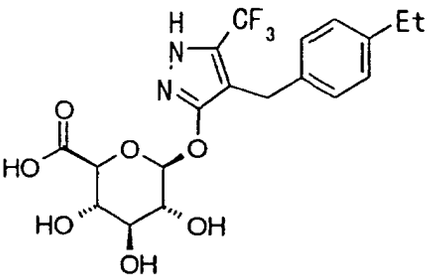
Synthesis of 4-[(4-isopropoxyphenyl) methyl]-5-methyl-1H-pyrazole-3-O- β -D-glucopyranoside

[0109] The product was synthesized in accordance with the methods described in Example 9 (yield point 253mg).
^{1}H-NMR (300MHz, DMSO-*d6*) δ : 7.07 (1H, d, J=8.4), 6.75 (1H, d, J=8.4), 5.12-5.20 (2H, m), 5.00 (1H, d, J=3.9), 4.92 (1H, d, J=3.9), 4.42-4.56 (2H, m), 3.58-3.68 (1H, m), 3.51 (2H, s), 3.42-3.54 (1H, m), 3.06-3.24 (4H, m), 2.00 (3H, s), 1.22 (6H, d, J=6.3) ESI-MS(m/z) : 409[$(M+H)^+$], 407[$(M-H)^-$].

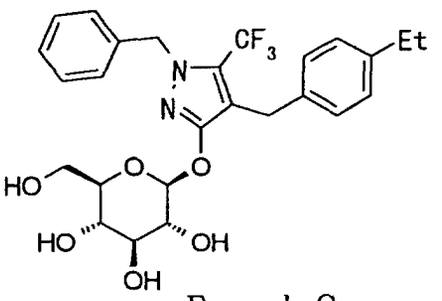
[0110] The structures of the compounds shown in Example 1 to 16 and Referential Example 1 are described as follows:



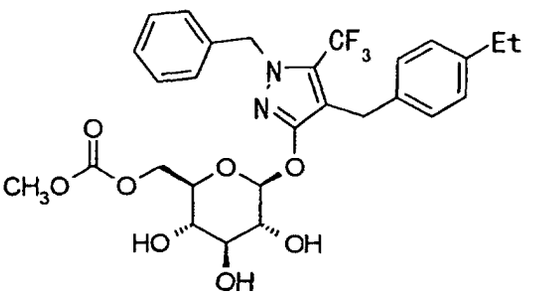
Example Compound 1



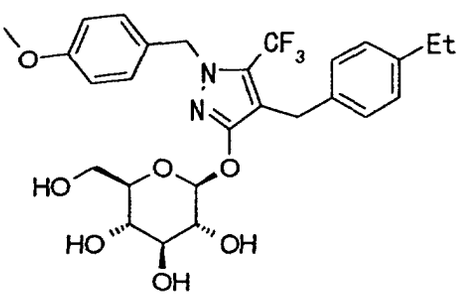
Example Compound 2



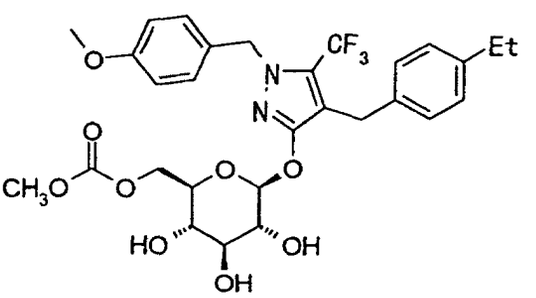
Example Compound 3



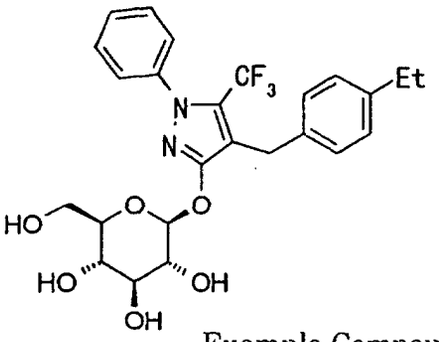
Example Compound 4



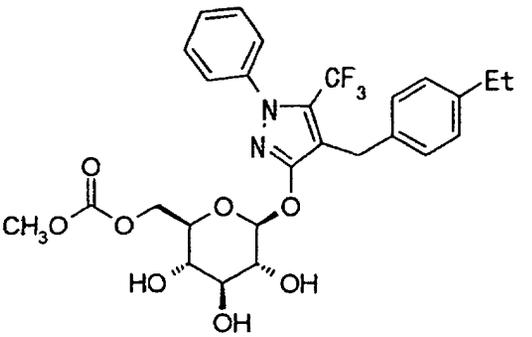
Example Compound 5



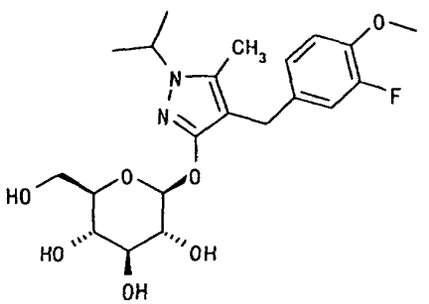
Example Compound 6



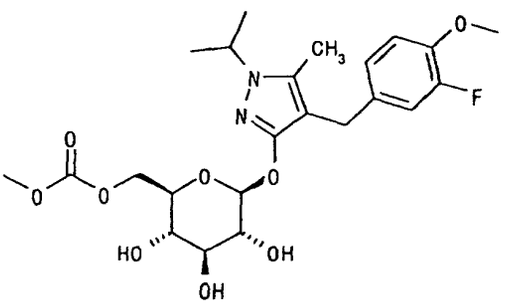
Example Compound 7



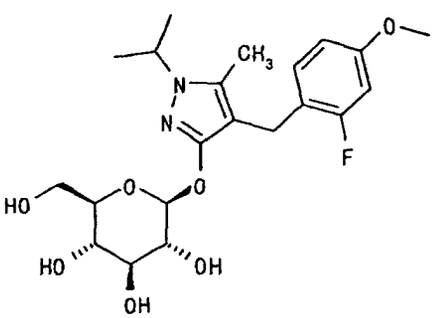
Example Compound 8



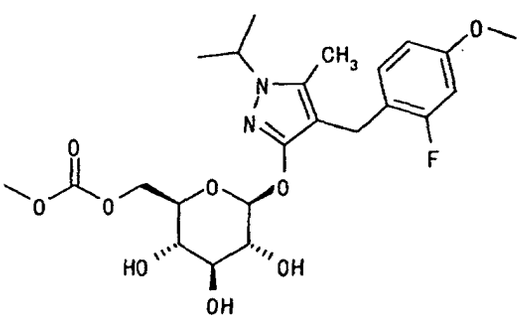
Example Compound 9



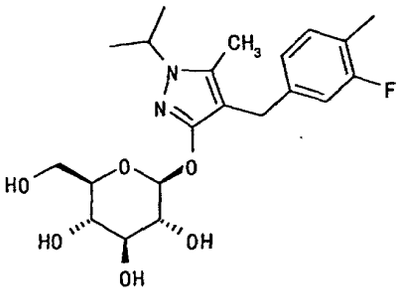
Example Compound 10



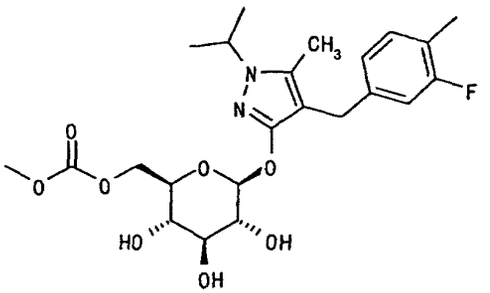
Example Compound 11



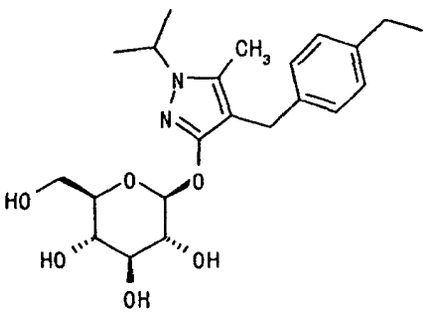
Example Compound 12



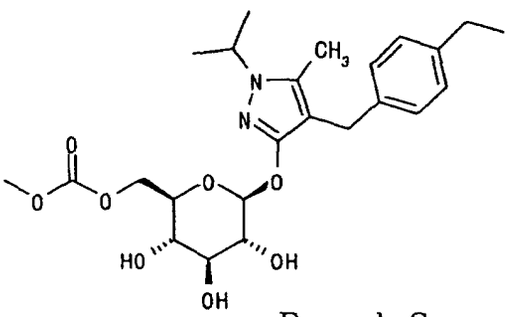
Example Compound 13



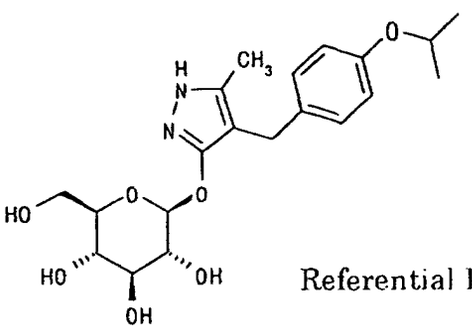
Example Compound 14



Example Compound 15



Example Compound 16



Referential Example Compound 1

Example 17

Evaluation of inhibiting activity on renal brush border membrane glucose uptake

[0111] The test compound was dissolved in 100mM Mannitol-10mM HEPES/Tris (pH7.4) and solutions having various concentrations were prepared.
Renal brush border membrane was prepared from a rat kidney and the solutions of the test compounds were added thereto and the product was incubated at 37°C for 30 minutes. Then ^{14}C-D-glucose was added and the mixture was incubated for 1 minute. After the reaction of glucose uptake was stopped by a solution containing 1mM of phloridzin, the activity of ^{14}C-D-glucose on ^{14}C was measured by a liquid scintillation counter. The intensity of inhibition was calculated by subtracting the amount of taken glucose that is independent on sodium from the amount of taken glucose of the object samples. The results of the evaluation are shown in Table 1.

Table 1

The test compounds	Inhibition intensity (concentration of the test compounds)
Example Compound 1	84% (10μM)
Example Compound 2	30% (100μM)

Example 18

Evaluation of activity on rat's sugar urine excretion

[0112] 5-week old male Wistar rats (purchased from Charles River Japan, Inc.) were used in the experiment after they were housed in a metabolic cage for about one week in advance. The test compounds were suspended in olive oil and 20mg/ml solution was prepared so that the dosage given per 1kg of the weight of the rats was 5ml.

[0113] After the rats were not fed for 4 hours, the test compounds were orally administered to them at 11 a.m. Their urine was collected, from that taken just after the administration to that taken 24 hours after the administration and its volume was measured. Then, the concentration of glucose in urine was measured by glucose oxidase method and urinary glucose excreted per a day and an individual was calculated. The results are shown in Table 2.

Table 2

	The dosage	The amount of excreted glucose in urine (mg)
Example Compound 4	100mg/kg	27
Example Compound 6	100mg/kg	59
Example Compound 8	100mg/kg	4.1
Example Compound 10	100mg/kg	734
Example Compound 14	100mg/kg	918
Example Compound 16	100mg/kg	598
	30mg/kg	294
	10mg/kg	263
	3mg/kg	28
Referential Example Compound 1	100mg/kg	14

[0114] It is obvious from the results shown above that the new pyrazole derivatives have higher inhibiting activity on glucose uptake and activity on urinary glucose excretion.

[0115] Especially, the inventors have found that the compounds wherein the substituents of hydroxyl group of glucopyranosyl group are lower alkoxycarbonyl group such as methoxy carbonyl group act as, so-called, a prodrug and the compounds in the present invention have high activity on urinary glucose excretion when they are orally administered.

[0116] The inventors also have found that the compounds wherein any one of R1, R2, R4, or R5 of general formula (1A) has a fluorine atom have particularly high activity on urinary glucose excretion. It is obvious from Example 10 and Example 14.

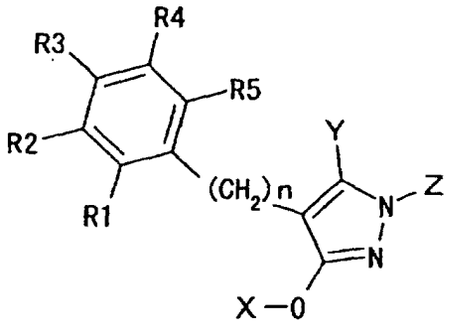
[0117] Further, they have found that the compound of Example 16 has particularly high activity on urinary glucose excretion. Example compound 16, which has high activity on urinary glucose excretion, still has high activity when the compound is orally administered in lower doses such as 30mg/kg or lower. The intended compound is not specifically described in WO01/16147.

[0118] Besides, Table 2 shows that the compounds of the present invention such as example compounds 10, 14 and 16 have much higher activity on urinary glucose excretion, as compared to Example 35 of WO01/16147 (Referential Example 1 of the present specification).

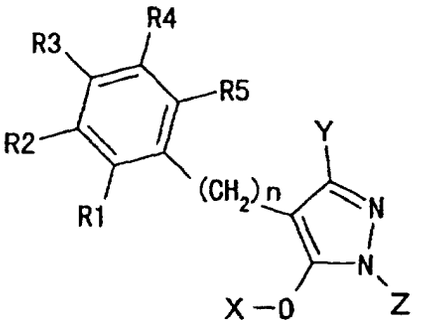
[0119] Namely, new pyrazole derivatives of the present invention show outstanding antidiabetic activity and, therefore, they are highly useful in the pharmaceutical industry.

Claims

1. Pyrazole derivatives of the following general formula (1A) or (1B) or pharmaceutically acceptable salts thereof:



(1A)



(1B)

wherein X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated or β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated and carboxyl group may be esterified; Y represents a lower alkyl group or perfluoro lower alkyl group; Z represents a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, aralkyl group or phenyl group; R1 to R5 may be the same or different and represent a hydrogen atom, lower alkyl group, perfluoro lower alkyl group, lower alkoxy group, perfluoro lower alkoxy group, lower alkylthio group, perfluoro lower alkylthio group, lower alkyl amino group, halogeno group, lower alkanoyl group, lower alkenyl group or lower alkynyl group, and n represents an integer from 0 to 3.

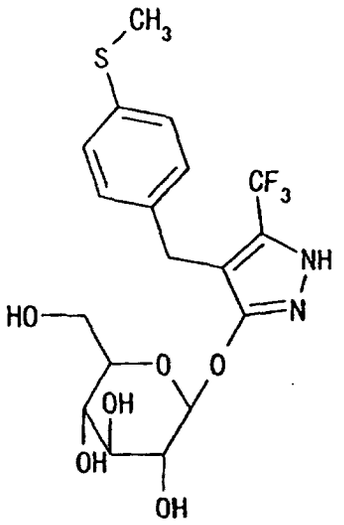
2. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, werein Y in the general formula (1A) or (1B) represents a trifluoromethyl group.

3. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the general formula (1A) or (1B), Y represents a trifluoromethyl group and n is 1.

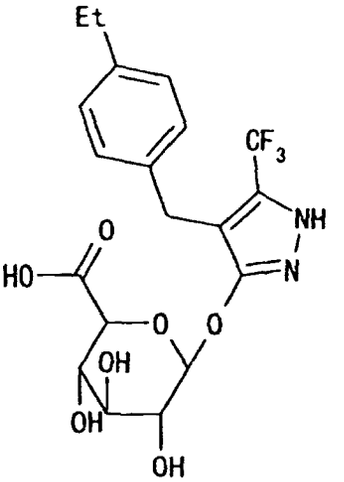
4. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a trifluoromethyl group, n is 1 and X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

5. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a trifluoromethyl group, n is 1 and X is a β -D-glucuronyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group and its carboxyl group may be esterified with lower alkyl group.

6. The compounds shown below or pharmaceutically acceptable salts thereof among the compounds of claim 1.



(2)



(3)

7. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group.

8. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with lower alkoxycarbonyl group.

9. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a lower alkyl group having 1 to 3 carbon atoms or perfluoro lower alkyl group having 1 to 6 carbon atoms; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents a hydrogen atom, lower alkyl group, unsubstituted aralkyl group or aralkyl group of which an aryl part at the 4th position is substituted or unsubstituted phenyl group; one of R1, R2, R4 and R5 is a halogeno group, or R1, R2, R4 and R5 are all hydrogen atom and R3 is a lower alkyl group, lower alkoxy group, lower alkenyl group or lower alkynyl group.

10. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group; R3 is a lower alkyl group and R4 or R5 is a fluorine atom.

11. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group; R3 is a lower alkoxy group and R4 or R5 is a fluorine atom.

12. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group and R3 is a lower alkynyl group.

13. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group; R3 is a lower alkynyl group and R4 or R5 is a fluorine atom.

14. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group and R3 is a lower alkenyl group.

15. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents an isopropyl group; R3 is a lower alkenyl group and R4 or R5 is a fluorine atom.

16. The pyrazole derivatives or pharmaceutically acceptable salts of claim 1, wherein, in the following general formula (1A) or (1B), Y represents a methyl group or trifluoromethyl group; n is 1; X represents a β -D-glucopyranosyl group, of which one or more hydroxyl groups may be acylated with the groups selected from alkanoyl group having 2 to 20 carbon atoms, lower alkoxycarbonyl group and benzoyl group; Z represents a hydrogen atom, isopropyl group, aralkyl group or phenyl group; one of R1, R2, R4 and R5 is a fluorine atom and R3 is a methyl group, ethyl group, methoxy group, vinyl group or ethynyl group.

17. The pyrazole derivatives of claim 1 selected from the group described below or pharmaceutically acceptable salts thereof.

4-((4-methylthiophenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-O- β -D-glucopyranoside;

4-((4-ethylphenyl) methyl)-5-(trifluoromethyl)-1H-pyrazole-3-yl- β -D-glucopyranoside uronic acid;

4-[(4-ethylphenyl) methyl]-1-benzyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;

4'-[(4'-ethylphenyl) methyl]-1'-benzyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(4-ethylphenyl) methyl]-1-[(4-methoxyphenyl) methyl]-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;

4'-[(4-ethylphenyl) methyl]-1'-[(4'-methoxyphenyl) methyl]-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(4-ethylphenyl) methyl]-1-phenyl-5-trifluoromethyl-1H-pyrazole-3-O- β -D-glucopyranoside;

4'-[(4'-ethylphenyl) methyl]-1'-phenyl-5'-trifluoromethyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(3-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O-β -D-glucopyranoside;

4'-[(3'-fluoro-4'-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(2-fluoro-4-methoxyphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O-β -D-glucopyranoside;

4'-[(2-fluoro-4-methoxyphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside;

4-[(3-fluoro-4-methylphenyl) methyl]-1-isopropyl-5-methyl-1H-pyrazole-3-O-β -D-glucopyranoside; and

4'-[(3'-fluoro-4'-methylphenyl) methyl]-1'-isopropyl-5'-methyl-1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside.

18. The pyrazole derivatives of claim 1 selected from the group described below or pharmaceutically acceptable salts thereof.

4-[(4-ethylphenyl) methyl]-1-isopropyl-5'-methyl-1H-pyrazole-3-O- β -D-glucopyranoside; and

4'-[(4-ethylphenyl) methyl]-1'-isopropyl-5'-methyl- 1H-pyrazole-3'-O-(6-carbomethoxy)- β -D-glucopyranoside.

19. A pharmaceutical composition comprising the pyrazole derivatives of claim 1 or pharmaceutically acceptable salts thereof.

20. A pharmaceutical composition for the treatment of diabetes which comprises the pyrazole derivatives of claim 1

or pharmaceutically acceptable salts thereof.

21. A urinary sugar excretion inducer comprising the pyrazole derivatives of claim 1 or pharmaceutically acceptable salts thereof.

22. Use of the pyrazole derivatives of claim 1 or pharmaceutically acceptable salts thereof for producing pharmaceutical compositions which reduce renal glucose reabsorption.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09555

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07H17/02, A61K31/7056, A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07H17/02, A61K31/7056, A61P3/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY (STN), CAPLUS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5264451 A (AMERICAN HOME PRODUCTS CORPORATION), 23 November, 1993 (23.11.1993) & US 5274111 A	1-22
A	KENNETH L.KEES, et al., New Potent Antihyperglycemic Agents in db/db Mice: Synthesis and Structure-Activity Relationship Studies of (4-Substituted benzyl)(trifluoromethyl)pyrazoles and pyrazolones, J. Med. Chem., 1996, Vol. 39, No. 20, pp.3920-3928	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January, 2002 (21.01.02)	29 January, 2002 (29.01.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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